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THE OLFACTORY-PAROTID REFLEX

STUDY OF ONE HUNDRED AND FIFTY PATIENTS WITH DISORDERS OF THE CENTRAL NERVOUS SYSTEM; A PRELIMINARY REPORT

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In the course of our investigations on the sense of smell, the possibility of obtaining an objective method of measuring olfactory function was carefully considered. With that object in view, the effects of odorous substances on the secretory rate of the parotid glands were investigated, and the results obtained in normal subjects were described in a recently published paper.[1] Furthermore, we made studies of the resting activity of the parotid glands and of the effects of an odorous substance, citral, on the volume of secretion of each gland in persons with disorders of the central nervous system. A preliminary report of these investigations is herewith given.

The rate of secretion of the parotid glands in normal persons has been studied and described by Winsor,[2] Strongin and Korchin. They showed that the rate of secretion is fairly regular and that the average resting rate in normal persons (uninfluenced by exterostimulation) varies between 0.02 and 0.15 cc. From their records, which they put at our disposal, we have calculated for 50 subjects the average normal secretory rate of the two parotid glands and found it to be between 0.0421 and

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1. Elsberg, C. A.; Spotnitz, H., and Strongin, E. I.: The Effect of Stimulation by Odorous Substances upon the Amount of Secretion of the Parotid Glands, J. Exper. Psychol. **27**:59, 1940.

2. Winsor, A. L.: Conditions Affecting Human Parotid Secretion, J. Exper. Psychol. **11**:355, 1928.

0.0451 cc. per minute, that is, about 0.20 to 0.22 cc. for each five minute period. The average volume of fluid secreted in five minutes by each parotid gland was about 0.10 cc.

METHOD AND MATERIAL

The technic used for the stimulation with odors was that described in a paper recently published.[3] The apparatus and technic used for the collection and measurement of the parotid secretion were essentially those of Winsor and Strongin and their associated workers.

It is sufficient to indicate that a small disk, similar to the one developed by Lashley, is fastened by suction over the opening of each Stenson duct. From the inner chamber of each disk a small air-tight tube passes through the corner of the mouth and carries the parotid secretion to a calibrated glass tube marked off in hundredths of a cubic centimeter. We have sometimes used calibrated tubes marked off in thousands of a cubic centimeter.

The subject was seated on an easy chair and instructed to assume a comfortable position. In order to avoid distracting influences, the tests were made in a partly soundproof room in which there were only the examiner and his subject.

After the disks had been applied to the openings of Stenson's ducts and the conducting tubes had been connected to the calibrated glass tubes, a period of twenty to thirty minutes was allowed to elapse before the stream injection of the odorous substance was begun. During this period the amount of secretion from each parotid gland was recorded every thirty seconds. The object of this preliminary period was to allow the subject to become adapted to the presence of the disks and to determine the resting rate of secretions of each parotid gland.

The subject then received a stream injection of the odorous substance at the rate of 2,000 cc. per minute [3] into one or into both nasal passages for a period of five minutes. During this time, the amount of secretion from each parotid gland was recorded at thirty second intervals. After the stimulation was concluded the amount of secretion during the next fifteen minutes was also recorded. Then, if desired, the other nasal passage was similarly stimulated. Finally, several drops of a lemon solution were placed on the tongue in order to check on the proper location of the disks. Only those tests were considered valid in which, at the conclusion of the test, drops of lemon solution on the tongue produced an observable increase of secretion from each parotid gland. Some examples of the effects of bilateral and unilateral stimulation in normal persons are given in tables 4 and 5.

In another paper, we have indicated that if an odorous substance, such as citral, is introduced into one nasal passage by stream injection, there are a marked increase of secretion from the ipsilateral parotid gland and a less marked increase from the gland of the opposite side. In some instances ipsilateral hypersecretion was associated with contralateral hyposecretion.

The process by which stimulation of the nasal passages by an odorous substance produces an alteration in the volume of secretion of the parotid glands is reflex—beyond the voluntary control of the subject. It is an

3. Elsberg, C. A., and Brewer, E. D.: The Sense of Smell: X. A Detailed Description of the Technique of Two Olfactory Tests Used for the Localization of Supratentorial Tumors of the Brain, Bull. Neurol. Inst. New York **4**:501, 1935.

unconditioned response, which we have called the olfactory-parotid reflex and which, as far as we know, has not previously been described in man.

Tests were made on patients with the following conditions:

	No.
Tumor of the brain, supratentorial	43
Tumor of the brain, infratentorial	12
Pituitary adenoma	9
Complete anosmia	3
Hysteria, psychoneuroses, etc.	25
Cerebral atrophy or hypoplasia	11
Grand mal	17
Aneurysm of the internal carotid artery	2
Cerebral thrombosis	3
Trigeminal neuralgia	4
Partial or complete division of the sensory root for trigeminal neuralgia	7
Facial paralysis, peripheral	4
Diffuse disease of the central nervous system	15
Non-neurologic diseases (?)	13

RESULTS

We have studied our results from several points of view: (1) information regarding the pathways traversed by the olfactory-parotid reflex; (2) significance of the variations in the resting secretory rate of the parotid glands in patients with disorders of the central nervous system; (3) significance of the variations in the volume of parotid secretion resulting from the olfactory-parotid reflex in patients with neurologic disorders.

1. *Pathways of the Olfactory-Parotid Reflex.*—(*a*) In 3 patients with complete anosmia as a sequence of fracture of the skull and in many others with unilateral loss or bilateral diminution of smell, the usual reaction to a stream injection of citral into one or both nasal passages occurred. The results of the tests in 3 patients with complete anosmia are presented in table 1.

Anosmia following trauma to the head is usually due to avulsion of the rootlets of the olfactory nerves from the cribriform plate of the ethmoid bone. That the olfactory-parotid reflex was present in persons with anosmia suggests that the afferent pathway for the reflex is not through the olfactory nerve. Though the element of odor may not be of significance, we have, nevertheless, called this reflex the olfactory-parotid reflex, since it is the result of the injection of an odorous substance, such as citral, into the nasal cavity.

(*b*) Thus far we have been able to study only a few patients in whom the branches of the trigeminal nerve or the entire sensory root has been

divided for the relief of trigeminal neuralgia. As an example, we shall give the data for a patient on whom the tests were made both before and after the differential section of the fibers of the second and most of the third branch of the trigeminal nerve.

The significant change in function of the parotid gland produced by the partial division of the trigeminal root on the right was that the left

TABLE 1.—*Olfactory-Parotid Reflex Responses in Patients with Complete Anosmia Following Head Injury* *

Case No.	Resting Secretory Rate, Cc.†		Secretory Rate on Nasal Stimulation, Cc.			
	R. P. G.	L. P. G.	R. P. G.		L. P. G.	
			Bilateral			
1	0.10	0.04	1.24		0.49	
2	0.16	0.18	0.23		0.33	
			Unilateral			
			Right Side		Left Side	
3 (loss of smell and taste)	0.53	0.43	1.00	0.31	0.42	0.74

* In this table and in the succeeding tables, R. P. G. means the right parotid gland; L. P. G., the left parotid gland.

† Resting secretory rate is expressed as the average volume secreted during a period of five minutes.

TABLE 2.—*Olfactory-Parotid Reflex Responses in a Patient with Right Trigeminal Neuralgia Before and After Differential Section of the Sensory Root of the Fifth Cranial Nerve*

	Before Root Section		After Root Section	
	R. P. G.	L. P. G.	R. P. G.	L. P. G.
Resting secretory rate, cc.	0.24	0.089	0.093	**0.28**
Secretory rate on stimulation of nasal mucosa on right with citral, cc.	1.37	0.03	0.57	0.79
Both glands	1.40		1.36	
Secretory rate on stimulation of nasal mucosa on left with citral, cc.	0.83	1.45	0.64	1.70
Both glands	2.28		2.34	
Total from both glands	3.68		3.70	

gland apparently took over the diminished activity of the right: (1) The resting activity of the right parotid gland, which had been greater, now became less than that of the left gland; (2) the total response of the two glands to stimulation remained practically constant, but the secretion of the right gland became less while that of the left gland became greater. These observations suggest that there are afferent fibers for the olfactory-parotid reflex in the trigeminal nerve. However, the results of our tests

were not always as clearcut as those cited. In some of the patients after division of the trigeminus nerve the olfactory-parotid reflex seemed little, if at all, interfered with.

(*c*) In some, but not in all, patients with facial paralysis of peripheral type (Bell's palsy) there was evidence to support the view that afferent fibers for the reflex run in the homolateral facial nerve, as shown by the results in the case cited in table 3.

2. *Significance of the Variations in the Resting Rate*[4] *of Parotid Secretion in Patients with Disorders of the Central Nervous System.*—That neurologic disease has a definite effect on the resting activity of the parotid gland was soon evidenced by our studies. We found that two types of abnormality occurred—the resting rate was abnormally low or abnormally high. Winsor and Strongin, in their studies on normal persons, had arrived at the conclusion that for each parotid gland the average resting rate varied between 0.02 and 0.15 cc. for a five minute

TABLE 3.—*Olfactory-Parotid Reflex Responses in a Patient with Paralysis of the Right Facial Nerve of Peripheral Type*

Resting Rate, Cc.		Secretory Rate on Unilateral Stimulation, Cc.			
		Right Side		Left Side	
R. P. G.	L. P. G.	R. P. G.	L. P. G.	R. P. G.	L. P. G.
0.48	0.13	0.05	0.26	0.06	0.29

period. They concluded that figures outside this range were abnormal. In order to learn whether, and if so how often, the secretory resting rate of the parotid gland was abnormal, we excluded all patients who had received drugs within thirty-six hours or who had partaken of food within two hours of the test. These patients were excluded because drugs and food may have considerable influence on the amount of secretion of the parotid glands. Of 64 patients with neurologic disease who had not received drugs or partaken of food for the periods mentioned, 17 had an abnormally high resting rate (i. e., above 0.15 cc. in five minutes) and 19 had an abnormally low resting rate (below 0.02 cc.). In summary, 56 per cent of the patients with neurologic disorders were found to have an abnormal resting rate of parotid secretion.

3. *Significance of the Variations in the Volume of Parotid Secretion Resulting from the Olfactory-Parotid Reflex in Patients with Neurologic Disorders.*—In table 4 we have given examples of the effects of the

4. The resting rate is the average volume of parotid secretion with the subject at rest and without stimulation of the nasal passages.

olfactory-parotid reflex in 3 normal subjects and in 3 patients as illustrations of the results obtained when the nasal mucosa is stimulated bilaterally with citral for five minutes.

Of the abnormal reactions, case 2 illustrates an abnormally high average resting rate and large volume response to nasal stimulation with citral, although the patient had been receiving phenobarbital, which is a depressant of parotid activity; case 16 illustrates an abnormally low resting rate and a comparatively normal response to stimulation with citral, and case 23 illustrates almost complete absence of secretion from the right parotid gland and absence of the olfactory-parotid reflex in a patient with a tumor of the right cerebellopontile angle.

In table 5 are recorded the olfactory-parotid reflex responses obtained from each gland on unilateral stimulation of the nasal mucosa in 3 normal subjects and in 5 patients with neurologic disorders.

TABLE 4.—*Olfactory-Parotid Reflex Responses on Bilateral Simultaneous Stimulation of the Nasal Mucosa with Stream Injection of Citral*

	Resting Rate, Cc.		Stimulated Rate, Cc.		Medication Before Test, Cc.
	R. P. G.	L. P. G.	R. P. G.	L. P. G.	
Normal subjects					
J. L.	0.04	0.11	0.29	0.77	None
D. D.	0.04	0.04	0.14	0.12	None
M. M.	0.06	0.11	0.40	0.57	None
Abnormal subjects					
Case 2: Astrocytoma of left frontotemporal region	**0.30**	**0.19**	**3.63**	**3.70**	Phenobarbital
Case 16: Astrocytoma of basal ganglia and third ventricle	**0.01**	**0.01**	0.20	0.83	None
Case 23: Tumor of right angle..	**0**	0.03	**0**	**0**	None

Of the abnormal reactions, cases 48 and 69 illustrate unusually high responses to stimulation, and cases 55 and 62 show that occasionally on nasal stimulation the contralateral gland may be more active than the ipsilateral gland. In both the latter cases, on stimulation of the nasal mucosa on the right side the response of the left gland was found to be greater than that of the right gland. Case 151 is an example of a low resting rate and almost complete absence of response from the left parotid gland. Also, on stimulation of the nasal mucosa on the left side the response from the right gland was almost entirely abolished.

In table 6 are listed the results obtained on a series of patients with unilateral supratentorial tumors, and in table 7 the results in a few patients with unilateral subtentorial tumors, of the brain.

The figures in tables 6 and 7 show that patients with tumor of the brain gave a number of types of reactions to nasal stimulation with citral.

TABLE 5.—*Olfactory Parotid Reflex Responses on Unilateral Stimulation of the Nasal Mucosa with Stream Injection of Citral*

	Resting Rate, Cc.		Rate on Stimulation of Nasal Mucosa, Cc.				Medication Before Test
			Right Side		Left Side		
	R. P. G.	L. P. G.	R. P. G.	L. P. G.	R. P. G.	L. P. G.	
Normal subjects							
H. S.	0.04	0.06	1.26	0.31	0.39	1.21	None
R. P.	0.03	0.04	0.30	0.20	0.16	1.91	None
D. K.	0.09	0.15	0.74	0.44	0.75	1.33	None
Abnormal subjects							
Case 48: Subchiasmal dermoid cyst	0.07	0.06	**5.20**	**2.47**	**196**	**4.57**	Roentgen therapy
Case 69: Encephalomalacia	0.05	0.03	**5.09**	**0.95**	**170**	**4.22**	Soluble phenobarbital U. S. P.
Case 55: Glioblastoma multiforme of right temporal region	0.03	0.11	0.12	**0.45**	0.03	0.39	Acetylsalicylic acid Caffeine
Case 62: Atrophy or hypoplasia of right cerebral hemisphere	0.11	0.05	0.13	**0.27**	0.41	0.69	None
Case 151: Tumor of left angle	**0.003**	**0.003**	0.11	**0**	**0.01**	**0**	Caffeine Acetylsalicylic acid

In some instances the reflex secretory response was unusually high; in others the stimulated rate of secretion was less than the resting rate—as though the stimulation had caused inhibition of secretion.

TABLE 6.—*Olfactory-Parotid Reflex Responses in Patients with Supratentorial Tumor of the Brain*

	Resting Rate, Cc.		Response to Nasal Stimulation, Cc.				
			Right		Left		Medication
Case No.	R. P. G.	L. P. G.	R. P. G.	L. P. G.	R. P.G.	L. P. G.	Before Test
Tumors of Right Cerebral Hemisphere							
40	0.01	0.01	0.26	0.01	0.11	0.82	None
46	0.02	0.01	0.29	0.16	0.14	0.48	Phenobarbital
55	0.03	0.11	0.12	0.45	0.03	0.39	Caffeine
59	0.05	0.01	1.45	0.33	0.99	2.44	None
79	0.06	0.09	0.18	0.23	0.37	0.33	Phenobarbital
87	0.15	0.10	0.03	0.02	0.06	0.01	None
108	0.05	0.06	0.16	0.06	0.03	0.06	None
114	0.03	0.09	0.08	0.01	0.04	0.02	None
155	0.12	0.36	1.41	0.99	0.28	1.83	None
Tumors of Left Hemisphere							
77	0.14	0.08	0.29	0.06	0.18	0.51	None
			0.94	0.27	0.29	0.41	
92	0.04	0.03	0.53	0.20	0.20	0.33	None
99	0.15	0.19	0.25	0.09	0.45	0.39	Orange juice
136	0.10	0.06	1.11	0.36	0.31	0.24	None
137	0.05	0.04	0.93	0.24	0.32	0.48	None
148	0	0.003	0.42	0	0.03	0.04	Phenobarbital

TABLE 7.—*Olfactory-Parotid Reflex Responses in Patients with Subtentorial Tumors of the Brain*

	Resting Rate, Cc.		Response to Nasal Stimulation, Cc.				
			Right		Left		Medication
Case No.	R. P. G.	L. P. G.	R. P. G.	L. P. G.	R. P.G.	L. P. G.	Before Test
Right Subtentorial Tumor							
Case 72.....	0	0.003	0.80	0.11	0.07	0.17	None
Left Subtentorial Tumor							
Case 76.....	0.02	0.01	0.07	0.03	0.04	0.01	None
Case 115.....	0.05	0.05	0.36	0.07	0.13	0.34	Phenobarbital
Case 151.....	0.003	0.003	0.11	0	0.01	0	.....
Case 156.....	0.01	0.42	0.01	0.46	0.01	0.90	Chocolate
Case 161.....	0.03	0.08	0.51	0.13	0	0.49	None

In table 8 we have averaged the results obtained in all of the patients in whom each nasal passage was separately stimulated.

These results show that in patients with neurologic disease on unilateral stimulation of the nasal mucosa with citral the ipsilateral parotid gland was on the average more than twice as active as the contralateral

gland. In patients with unilateral supratentorial tumor of the brain the relative quantity secreted by each gland changed. Furthermore, on the average the parotid gland contralateral to the brain tumor secreted a greater volume on contralateral nasal stimulation than the ispsilateral gland secreted on ipsilateral nasal stimulation. In the patients with subtentorial tumor of the brain, the reverse was true; on the average the parotid gland ipsilateral to the tumor of the posterior fossa gave a greater volume response to ipsilateral stimulation than did the contralateral gland to contralateral nasal stimulation. This difference between patients with supratentorial and those with subtentorial tumor suggests that the cerebral pathways for the olfactory-parotid reflex cross in their course from the cerebral cortex to the brain stem.

TABLE 8.—*Olfactory-Parotid Reflex Responses to Stimulation of Nasal Mucosa*

	Stimulation of Right Side		Stimulation of Left Side	
	R. P. G.	L. P. G.	R. P. G.	L. P. G.
Average response in 123 tests on patients with neurologic disorders	0.73	0.31	0.30	0.70
Average response in 7 tests on 6 patients with tumors of the left cerebrum	0.64	0.17	0.25	0.34
Average response in 9 tests on 9 patients with tumor of the right cerebrum	0.44	0.25	0.23	0.71
Average response in 5 tests on patients with tumor of left posterior fossa	0.21	0.14	0.04	0.35
Response in 1 test on a patient with a tumor of right posterior fossa	0.80	0.11	0.07	0.17

COMMENT

With the exception of Snarski's [5] article (1901), which reported that the injection of certain odorous substances into the nasal cavity of a dog produced an increase in secretion of the salivary glands, little information has been available regarding the effect of odorous substances on salivary secretion. Lashley [6] reported that odors had no effect on the rate of parotid secretion. However, from our studies it appears that the injection of an odorous substance, such as citral, into the nasal cavity produces a response from both glands, predominantly from the ipsilateral gland.

As regards the pathway of the reflex, we were able to confirm in man the original observation of Snarski on dogs, namely, that the olfactory

5. Snarski A. T.: Analiz normalnikh usloviy raboti slyunikh zhelyoz u sobaki [Analysis of the Normal Conditions for Salivary Activity in Dogs], Thesis, St. Petersburg, 1901.

6. Lashley, K. S.: Reflex Secretion of the Human Parotid Gland, J. Exper. Psychol. **1**:461, 1916.

nerve is not necessary for the reflex. In all of our patients with complete anosmia due to a peripheral lesion of the olfactory nerve the reflex was present. The fact that disturbances of the reflex occurred in patients with lesions of the trigeminal or the facial nerve suggests that these nerves are involved in the afferent arc of the reflex. Other investigators, notably Babkin [7] and Müller,[8] suggested that only the third branch of the trigeminal nerve was involved in any salivary reflex, but it is our impression that the first and second branches of this nerve are also involved. The observation that the seventh cranial nerve is involved in the reflex response is of considerable interest; it may be that this is related to the fact that the major superficial petrosal nerve joins the facial nerve at the geniculate ganglion. Investigation of the relation of the facial nerve to the reflex might make it possible to distinguish lesions peripheral from those central to the geniculate ganglion.

Some authors have discussed the possible significance of the pharyngeal branch of the vagus nerve and the sympathetic nervous system in the afferent arc of the reflex. Up to the present, we have no facts regarding this aspect of the subject.

Thus far we have considered only the afferent arc of the reflex. We have not discussed the effect of lesions of the efferent fibers of the reflex arc, nor have we investigated the question of the localization of the nuclei of the brain stem involved in the reflex.

That the cerebral cortex has a definite effect on salivary secretion is well known since the animal investigations of Pavlov,[9] von Bechterew [10] and others. Cerebral lesions, as we have shown, produce alterations in the resting rate of secretion, and also in the reflex response, of the parotid glands in a high percentage of patients with neurologic disorders. As far as man is concerned, it appears likely that the contralateral cerebral hemisphere has a greater effect on the activity of a parotid gland than the ipsilateral hemisphere. In general, it was our impression that the function of the parotid gland contralateral to the cerebral lesion was more unstable and more abnormal than the function of the parotid gland ipsilateral to the lesion. The fact that the contralateral parotid gland was often overactive or underactive may eventually be correlated with the

7. Babkin, B. P.: Die äussere Sekretion der Verdauungsdrüsen, in Gildemeister, M.; Goldschmidt, R.; Neuberg, C.; Parnas, J., and Ruhland, W.: Monographien aus der Gesamtgebiet der Physiologie der Pflanzen und der Tiere, Berlin, Julius Springer, 1928.

8. Müller, L. R.: Lebensnerven und Lebenstriebe, ed. 3, Berlin, Julius Springer, 1931.

9. Pavlov, I. P.: Lectures on Conditioned Reflexes, translated from the Russian by W. H. Gantt, New York, International Publishers Co., Inc., 1928.

10. von Bechterew, W.: Die Funktionen der Nerven Centra, Jena, Gustav Fischer, 1911, vol. 3.

recent observation of Hare and Geohegan [11] and Bronk and his co-workers [12] that, depending on the quantitative value of the cortical stimulus, excitation or inhibition may be produced from the same cortical area of the brain. Further study is necessary to determine whether the temporal lobe has any special significance as a cerebral center for the control of the volume of secretion of the parotid gland.

SUMMARY AND CONCLUSIONS

The resting rate of secretion of the parotid gland was found to be abnormal in 56 per cent of a series of 64 patients with neurologic disorders.

Stream injection of the odorous substance, citral, into the nasal cavity produced a definite increase in the volume of secretion from the ipsilateral parotid gland in normal human beings. The effect on the contralateral parotid gland was less marked.

It is suggested that the reflex response of the parotid glands on stimulation of the nasal mucosa with odorous substances be called the olfactory-parotid reflex. There is evidence to support the view that the afferent pathway of the reflex is not in the first cranial nerve but involves the fifth and seventh cranial nerves.

Neurologic disorders produce overactivity and underactivity of the reflex. There is some evidence that the cerebral pathways which affect the reflex cross in their course from the cerebral cortex to the brain stem.

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DISCUSSION

DR. FREDERICK L. REICHERT, San Francisco: Were any studies made in cases in which the ninth nerve had been cut? Apparently the secretory fibers to the parotid gland are supplied through the seventh and ninth cranial nerves.

DR. H. SPOTNITZ, New York: Yes; we examined a patient who had a section of the right ninth and right fifth nerves and the right sympathetic nerve chain. This patient did not have the reflex on either side.

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11. Hare, K., and Geohegan, W. A.: The Influence of Frequency of Hypothalamic Stimulation upon the Response, Am. J. Physiol. **126**:524, 1939.

12. Bronk, D. W.; Pitts, R. F., and Larabee, M.G.: Rôle of Hypothalamus in Cardiovascular Regulation, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:323, 1940.

ELECTROENCEPHALOGRAPHIC STUDIES ON NEUROSYPHILIS

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Electroencephalographic study of the human brain has not yet advanced beyond the descriptive stage. Records are described as normal or abnormal depending on their occurrence in normal control subjects or in patients with known pathologic conditions of the central nervous system. The ultimate goal of investigators in this field is to correlate the electroencephalographic patterns with neurophysiologic processes. Progress will come largely through animal experimentation and careful study of the electroencephalographic patterns associated with disorders of the central nervous system in which the location and type of lesions are known. It was with this problem in mind that the present study on neurosyphilis was begun. Furthermore, it is of practical interest to determine whether the electroencephalogram can be of any aid in the diagnosis of neurosyphilis, in the determination of the type of involvement or in the prognosis before or during the course of therapy.

MATERIAL

This report is a preliminary analysis of the single or repeated electroencephalographic records obtained during the past two and one-half years on 175 patients from the neurosyphilis clinic of the Boston Psychopathic Hospital.

From the patients who remained in the hospital for fever therapy and from those who continued chemotherapy in the outpatient clinic repeated tracings were obtained at intervals of one to three months. Some patients who had been transferred to other institutions were brought back for follow-up records.

METHOD

The records were obtained with a six channel, ink-writing oscillograph of the Grass type. Three electrodes were placed over the frontal, the precentral and the occipital region of each hemisphere, the indifferent electrode being placed

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over the mastoid. Two types of tracings were obtained: (*a*) six simultaneous recordings from the frontal, precentral and occipital areas of the two hemispheres grounded to the indifferent mastoid electrode, and (*b*) six simultaneous bipolar recordings with leads arranged as follows: (1) left frontal to left precentral, (2) right frontal to right precentral, (3) left precentral to right precentral, (4) left precentral to left occipital, (5) right precentral to right occipital and (6) left occipital to right occipital. The records were taken with the patient reclining and with the eyes closed.

RESULTS

The records thus obtained were divided into three groups, normal, borderline normal and abnormal (fig. 1), the basis of normality and

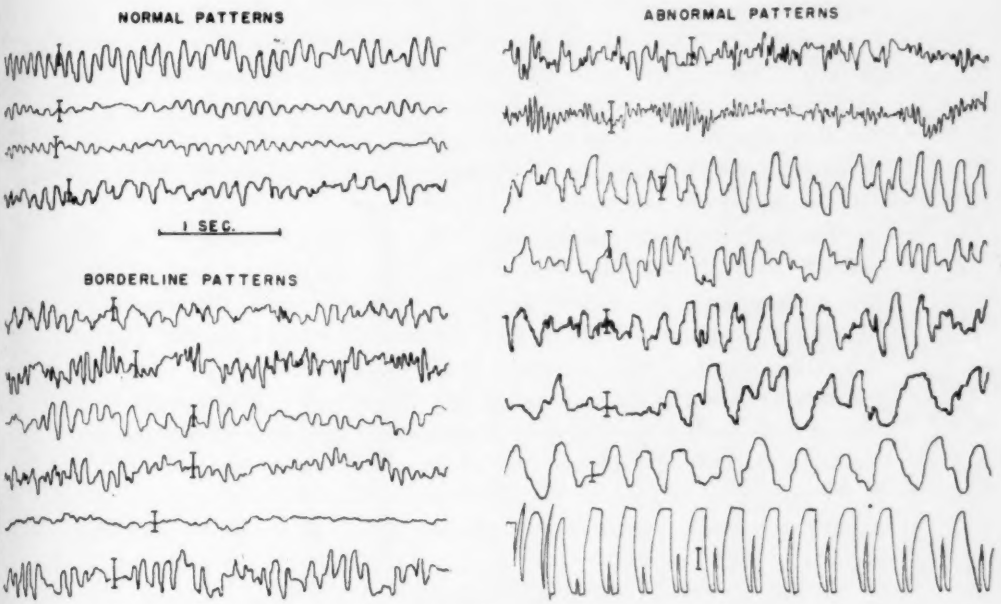


Fig. 1.—Samples of normal, borderline and abnormal patterns, the degree of normality or abnormality of the patterns having been determined by their occurrence in normal control subjects and in patients with known lesions of the central nervous system.

In this figure and in the following figures, the vertical ink line drawn through the tracing is equivalent to 50 microvolts, while the horizontal line represents one second of recording.

abnormality being determined by the occurrence of similar patterns in normal controls and in patients with known lesions of the central nervous system. There was considerable variation in the records of each group (fig. 1), particularly in the borderline and the abnormal group. Normal records had a basic frequency pattern of 8 to 12 cycles per second, which

from time to time might be interrupted by or have superimposed on them low voltage, rapid activity. The borderline records showed a mild degree of disorganization, due to irregular contours of the normal frequency cycles, to a greater predominance of low voltage, rapid activity and to occasional slow cycles. These borderline records correspond to the "questionable normal" tracings illustrated in the Gibbs's "Atlas on Electroencephalography." [1] The abnormal records showed a breaking down of the normal pattern. The pattern of some was disorganized, having slow, rapid and normal cycles of varying contour, frequency and amplitude. Other abnormal records showed a predominance of well organized rapid activity (usually 18 to 30 cycles per second), the frequency of which remained constant in an otherwise normal frequency pattern. Again, the rapid activity might show less consistency, with variation both in the frequency and in the amplitude of the rapid cycles. Another type of abnormal record was that in which slow activity predominated, which might be of either constant or changing frequency (less than 8 cycles per second).

The first electroencephalographic tracings taken on each of the 175 patients with neurosyphilis (both treated and untreated) were divided into normal, borderline normal and abnormal patterns and the percentage distribution compared with that of the records of 215 normal control subjects (fig. 2). Approximately 70 per cent of the records from the controls were normal, in contrast to only 19 per cent of the records from the patients with neurosyphilis. Twenty-four per cent of the records from the controls and 28 per cent of the records from the patients fell in the borderline range. While only 7 per cent of the control group had abnormal records, 53 per cent of neurosyphilitic patients had abnormal records.

Of the 175 patients with neurosyphilis, 124 had dementia paralytica, 20 tabes, 8 optic nerve atrophy, 11 the juvenile type of dementia paralytica and 12 meningovascular syphilis. The percentage distribution of the normal, borderline and abnormal records for each type of neurosyphilis is illustrated in figure 3. The significance of the percentage distribution of the records in the cases of optic nerve atrophy, juvenile dementia paralytica and meningovascular neurosyphilis is questionable because of the small number of cases. Nevertheless, the high percentage (about 90 per cent) of borderline and abnormal records in the cases of juvenile dementia paralytica and optic nerve atrophy is striking. This high incidence of abnormal records in the cases of tabes and optic nerve

1. Gibbs, F. A., and Gibbs, E. L.: Atlas on Electroencephalography, Cambridge, Mass., Lew A. Cummings Co., 1941.

atrophy is of particular interest because the lesions do not lie primarily in the cortex, as they do in dementia paralytica.

As shown in figure 2, 81 per cent of the records from the patients with neurosyphilis were classified as borderline normal and abnormal. Figure 4 illustrates the lack of consistency in the appearance of these patterns. Although no two patterns were identical, for convenience we arbitrarily chose as samples twelve patterns and classified each of the first records obtained on the 175 patients with the sample which it most nearly resembled. No one type of pattern appeared in

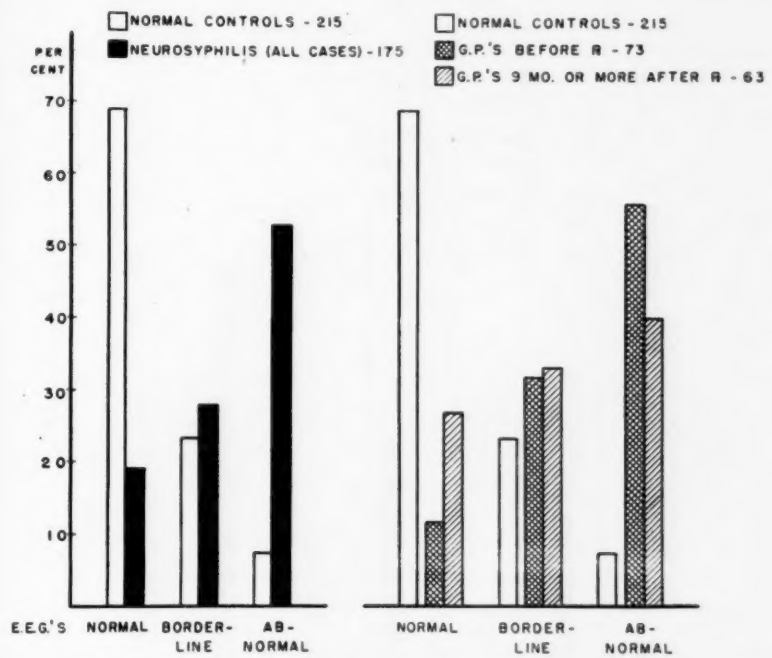


Fig. 2.—The left hand part of the graph illustrates the much higher percentage of normal records in the group of control subjects and the much higher percentage of abnormal records in the group of neurosyphilitic patients. The right hand graph illustrates an increase in the percentage of normal records and a decrease in the percentage of abnormal records of patients with dementia paralytica (*G. P.'s*) after nine months or more of treatment.

more than 21 per cent of the total number of patients. The samples illustrated were all taken from patients with dementia paralytica, with the exception of sample 12, which was obtained from a patient with juvenile dementia paralytica. A brief description of the twelve samples (fig. 4) follows.

Sample 1: A normal pattern with cycles of uniform contour and a frequency of 11 cycles per second.

Sample 2: A normal pattern with less uniformity in the pattern, with some traces of low voltage, rapid activity but with a basic normal frequency of 9 cycles per second.

Sample 3: A borderline record with more marked disorganization of the pattern than in the two preceding samples, there being scattered low voltage, rapid activity, random low voltage, slow cycles of irregular contour and scattered normal frequency cycles.

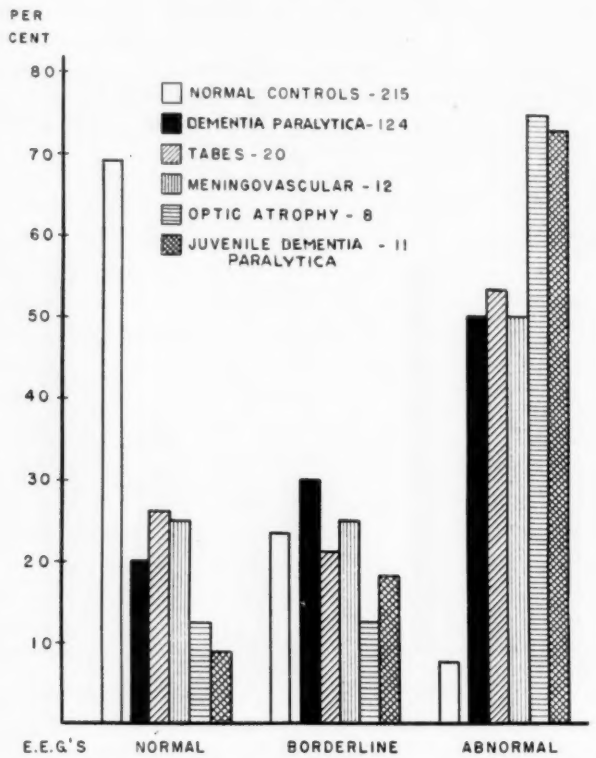


Fig. 3.—The percentage of normal, borderline and abnormal records of patients with various types of neurosyphilis, as compared with those of normal controls.

Sample 4: A borderline record with predominance of low voltage, rapid activity.

Sample 5: An abnormal pattern with short runs or groups of well organized rapid activity, having a frequency between 17 to 20 cycles per second and an amplitude greater than 25 microvolts.

Sample 6: An abnormal pattern with a basic rapid frequency pattern from the frontal and precentral leads, averaging 20 to 25 cycles

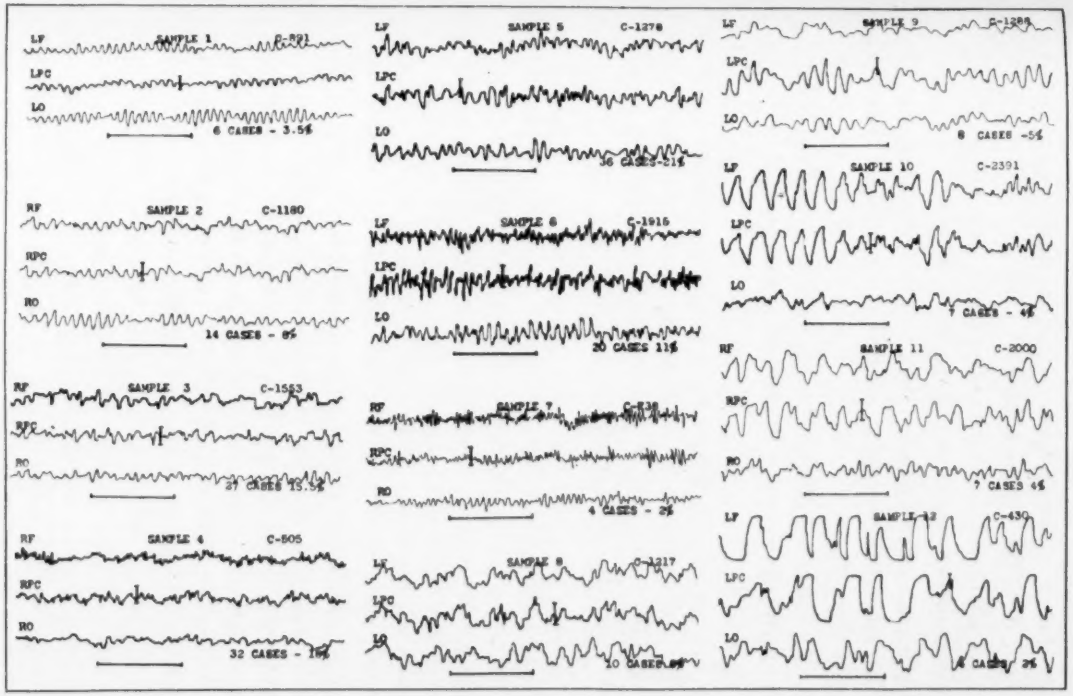


Fig. 4.—Samples of twelve types of records, including normal, borderline and abnormal tracings, demonstrating the lack of consistency in electroencephalograms of neurosyphilitic patients. Each sample has three simultaneous recordings from the frontal, the precentral and the occipital region. The data given in the lower right corner represent the number and percentage of patients in the total series of 175 neurosyphilitic patients whose first records resembled the sample. In other words, 6, or 3.5 per cent, of the first records obtained on the 175 patients with neurosyphilis resembled sample 1.

per second, with considerable inconsistency in both the amplitude and the frequency of the rapid cycles.

Sample 7: An abnormal pattern with a well organized and uniform rapid frequency pattern of 30 cycles per second from the frontal and precentral leads, but a slower frequency pattern, averaging 15 to 17 cycles per second, from the occipital leads.

Sample 8: An abnormal pattern showing many slow cycles of irregular contour with superimposed low voltage, rapid activity.

Sample 9: An abnormal pattern with lack of consistency in the amplitude of the various cycles and a frequency averaging 7 cycles per second.

Sample 10: An abnormal pattern showing random occurrence as well as runs of slow, high voltage cycles of uniform frequency—3.5 cycles per second.

Sample 11: An abnormal pattern with slow, high voltage cycles of irregular contour, the frequency of which varies from 2 to 5 cycles per second, many of the cycles having superimposed on them more rapid activity, the slow activity being most marked from the precentral and occipital leads.

Sample 12: An abnormal pattern with high voltage, slow, 1.5 to 3 per second cycles and scattered rapid spikes. This pattern has some similarity to the spike and wave activity, which is most commonly associated with the epileptic disorders.

The same lack of consistency in the type of the pattern was observed in cases of tabes, optic nerve atrophy, meningovascular syphilis and juvenile dementia paralytica. This lack of consistency in the electroencephalographic tracings, not only in neurosyphilis in general but in the clinical subtypes, does not permit one to place any diagnostic significance on the character of the electrical potentials in these disorders. This point is further strongly supported by the fact that the same patterns are found in connection with other neuropsychiatric disorders. Rapid activity, resembling that seen in samples 5, 6, and 7, is frequently encountered in cases of manic-depressive disorders, agitated depressions of middle age, schizophrenia and occasionally epilepsy.[2] Likewise, the slow activity illustrated in samples 8 to 12 is found in a variety of neurologic conditions, including epilepsy.

It is of interest to observe how often these twelve types appeared in each of the main neurosyphilitic syndromes, i. e., dementia paralytica,

2. Finley, K. H., and Campbell, C. M.: Electroencephalography in Schizophrenia, Am. J. Psychiat. **98**:374-381, 1941.

tabes, meningovascular syphilis, optic nerve atrophy and juvenile dementia paralytica (fig. 4). The percentage incidence of each of these syndromes for each sample type of electroencephalogram was as follows:

	Dementia Paralytica, %	Tabes, %	Meningo-vascular Syphilis, %	Optic Nerve Atrophy, %	Juvenile Dementia Paralytica, %
Sample 1	3	10	0	0	0
Sample 2	10	5	0	0	9
Sample 3	14	20	34	12.5	9
Sample 4	20	20	25	12.5	9
Sample 5	23	20	17	25	9
Sample 6	9	15	8	50	9
Sample 7	2	0	8	0	0
Sample 8	6	5	0	0	9
Sample 9	4	0	0	0	0
Sample 10	3	5	0	0	19
Sample 11	5	0	8	0	0
Sample 12	1	0	0	0	27

Of the 124 patients with dementia paralytica from whom we obtained electroencephalographic records, 73 had previously received either no treatment or very inadequate treatment. From 63 of the patients with dementia paralytica records were obtained nine months or more after the beginning of fever therapy. A comparison of the percentage distribution of the normal, borderline and abnormal electroencephalographic records shows that the treated group presented 16 per cent fewer abnormal and 15 per cent more normal records than did the untreated group (fig. 2).

In table 1 the type of electroencephalographic tracings is tabulated against the severity of the clinical picture for the 73 untreated patients. This table shows that in the group with clinically mild disease the majority of the tracings were of borderline normality. In the group with disease of intermediate clinical severity more records fell in the abnormal range, while in the group with a severe clinical picture a still greater number were on the abnormal side. Taking this group as a whole, the more severe the clinical picture the more abnormal the record was likely to be. There are exceptions, the explanation of which constitutes a problem in itself and requires a longer period of study. Table 2 deals with the 63 patients for whom we have electroencephalographic tracings after nine months or more of treatment. The table shows a shift of the clinical picture and the electroencephalographic tracings of these patients toward the side of improvement. There are many exceptions here, also, which we may hope to explain after further observations and longer follow-up studies.

Seven of the 9 patients for whom the original record was normal (table 2) have shown clinical improvement. Of 12 patients with abnormal electroencephalograms showing a predominance of slow activ-

TABLE 1.—*Electroencephalographic Tracings Tabulated Against the Severity of the Clinical Pictures of Seventy-Three Untreated Patients* *

Clinical Classification	Electroencephalogram			Total	Percentage
	Normal	Borderline	Abnormal		
Mild	2	7	3	12	16.5
Intermediate	5	8	14	27	37
Severe	2	8	24	34	46.5
Total	9	23	41	73	
Percentage	12.3	31.5	56.2		100

* In the group with clinically mild disease the majority of tracings are borderline, in the group with disease of clinically intermediate severity more fall into the abnormal range and in the group with clinically severe disease a still greater number are abnormal.

TABLE 2.—*Electroencephalographic Tracings Tabulated Against the Clinical Results for Sixty-Three Patients with Dementia Paralytica After Nine or More Months of Treatment* *

Clinical Result	Electroencephalogram			Total	Percentage
	Normal	Borderline	Abnormal		
Remission	9	6	2	17	27
Improvement	7	12	10	29	46
No improvement or progression	1	3	13	17	27
Total	17	21	25	63	
Percentage	27	33	40		100

* In general when there is clinical improvement there is a comparable change in the electroencephalographic tracing.

TABLE 3.—*Electroencephalographic Tracings Tabulated Against the Clinical Results for Eighteen Treated Patients Who Are Serologically Negative* *

Clinical Result	Electroencephalogram			Total
	Normal	Borderline	Abnormal	
Remission	4	5	1	10
Improvement	6	1	..	1
No improvement	..	1	..	1
Total	10	7	1	18

* A high percentage of normal records appear.

ity, 7 are unimproved or worse, 2 are dead and only 3 have shown improvement. This indicates that patients whose records are normal respond better to treatment than patients whose electroencephalographic tracings show slow activity.

In the series of treated patients (table 3), 18 now give negative serologic reactions and no longer require active chemotherapy. With the

exception of 1 patient, all of these are clinically improved or the disease is in remission. Of this group the electroencephalographic tracings were normal in 10, borderline in 7 and abnormal in 1 (table 3). This suggests a possible correlation between the electroencephalographic and the serologic status. It must be borne in mind that the serologic change is slow and may require several years to accomplish. Therefore the character of the electroencephalogram after treatment may be dependent not only on the serologic condition but on the process of healing, which may continue over a longer period.

The changes in the electroencephalographic patterns which take place under treatment and their relationship to the clinical course are illustrated in a series of tracings (fig. 5) obtained from 9 patients with neurosyphilis. *A* and *B* were patients with dementia paralytica whose pretreatment tracings were extremely abnormal, showing very slow, high voltage activity. It is to be noted that there was a dramatic change for the better in the tracings after treatment, the slow activity being replaced by normal and rapid frequency cycles. In both instances there was marked improvement in the clinical picture to correspond with the change in the electroencephalogram. *C*, a patient with dementia paralytica, had a series of four moderately abnormal tracings, the main abnormal feature being the predominance of rapid activity. No significant change in the quality of the tracings occurred after the first record, at which time treatment was begun. Clinically the patient improved. This is a case in which the electroencephalogram remained unchanged even though there was clinical improvement. *D*, a patient with dementia paralytica, had a moderately abnormal pattern in the first two records preceding fever treatment but showed improvement in the two later records. The final tracing was normal. Clinically the patient remained unimproved. *C's* electroencephalographic tracings remained unchanged with clinical improvement; in the case of *D* the reverse was true—the electroencephalogram improved, but the clinical condition remained unchanged. *E*, a patient with dementia paralytica, showed predominance of slow, high voltage activity in the first record. The next two tracings, obtained after fever therapy, showed definite improvement in the quality. During the period in which these three records were obtained the patient did not improve clinically, even though there was distinct improvement in the character of the electroencephalographic tracing. Slow activity reappeared in the final tracing. Shortly thereafter the patient had a clinical relapse and died. *F*, a patient with tabes, had a predominance of slow, high voltage activity in the first tracing. Subsequent records, taken after fever treatment, showed a change toward normal. Clinically the patient exhibited marked improvement in tabetic symptoms. The change in the tracings in this case of tabes is similar to that in the first 2 cases of dementia paralytica (*A* and *B*). A patient with juvenile dementia paralytica showed marked

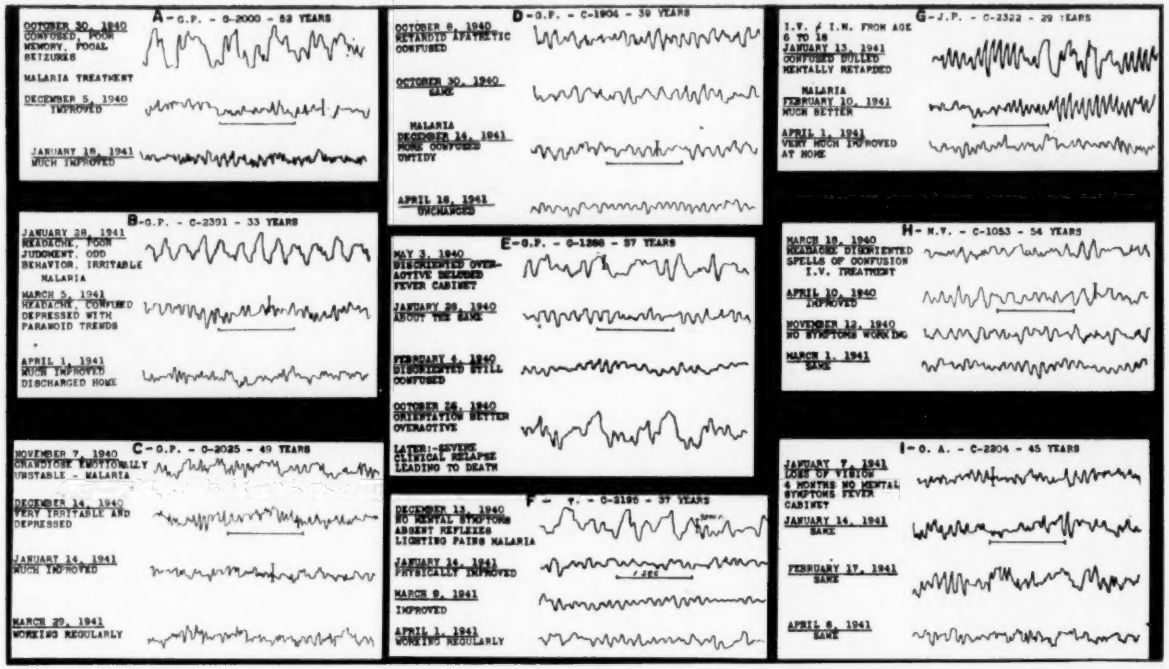


Fig. 5.—A series of records (all left precentral) from 9 patients with neurosyphilis, illustrating the changes in the electroencephalographic tracing occurring during and after treatment.

improvement both clinically and in the character of the electroencephalographic record (*G*) after fever therapy. It is to be noted, however, that this represents an exceptional result for a patient with this form of the disease. *H*, a patient with meningovascular neurosyphilis, showed mild abnormal changes in the tracings in the form of scattered cycles with a frequency of 5 to 7 per second. This pattern was still present in the second tracing after intravenous treatment had been started and clinical improvement obtained. The third tracing, obtained after eight months of continuous treatment, showed a decrease in the slow activity, and the last record, obtained after fourteen months of treatment and continued clinical improvement, was normal. *I*, a patient with optic tabes, showed a series of four patterns all essentially the same, exhibiting disorganized rapid activity. The absence of change in the patterns corresponded to the lack of improvement in vision, although there was considerable physical improvement.

COMMENT

Berger,[3] in two reports on electroencephalographic tracings associated with neuropsychiatric disorders, included 39 cases of dementia paralytica. He observed abnormal tracings in many of these cases and found no consistency in the type of pattern. This is confirmed by our studies. He was particularly impressed by two types of patterns: (1) a pattern of rapid activity with high amplitude, and (2) a pattern in which the activity changed from rapid to slow. Samples *6* and *10*, respectively, of figure 4 are illustrations of these patterns obtained from our series. In their "Atlas on Electroencephalography" Gibbs and Gibbs show samples of patterns from 4 cases of dementia paralytica, all of which were different in character and 1 of which they termed normal. There are no other published data dealing specifically with electroencephalographic patterns in neurosyphilis, although A. E. Bennett, in a demonstration on electroencephalography at the meeting of the American Psychiatric Association held in Richmond, Va., in May 1941, illustrated, among other things, a series of electroencephalographic tracings from several cases of dementia paralytica in which the character of the pattern improved after antisyphilitic treatment.

The present study, in which one or more tracings were obtained on 175 patients with neurosyphilis, demonstrates that there is nothing characteristic in the patterns of dementia paralytica, tabes, juvenile dementia paralytica, optic nerve atrophy and meningovascular syphilis. Furthermore, any one of the patterns herein described may be found in any one of several other neuropsychiatric disorders. Therefore it is clear that the diagnosis of neurosyphilis cannot be made from electroencephalographic tracings.

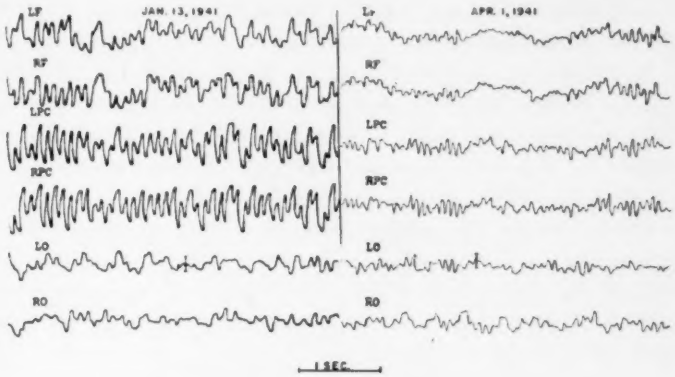
3. Berger, H.: Ueber das Elektrenkephalogram des Menschen: III, Arch. f. Psychiat. **94**:16-60, 1931; VI, ibid. **99**:555, 1933.

Several features of the records obtained from the patients with juvenile dementia paralytica are worthy of special comment. Of the 11 patients in this group, 8 had abnormal tracings, most of which were extremely abnormal, 2 had borderline records and only 1 had a normal record. The last patient had had six years of active treatment, the serologic reactions were negative and the disease was clinically arrested at the time the record was made. Slow, high voltage cycles were more common in the records of patients with juvenile dementia paralytica than in those of patients with any of the other types of neurosyphilis. This slow activity has been more resistant to modification by treatment than other abnormal patterns associated with other types of neurosyphilis. This correlates closely with the usual poor clinical response to treatment of juvenile dementia paralytica.

Because the lesions of dementia paralytica occur predominantly in the cortex while those of tabes are found chiefly in the spinal cord and midbrain, one would expect to find a greater degree of abnormality in the brain potentials in the former than in the latter disease. Our present studies, as has been pointed out, show that this is not the case. In the absence of clinically significant cortical lesions in tabes, it would seem that the lesions in the region of the midbrain or diencephalon are most likely responsible for the abnormal electrical activity recorded over the cortex. On the other hand, in dementia paralytica it is a reasonable assumption that the abnormal activity is due primarily to the cortical lesions. Yet if this assumption were true there should be a difference in the character of the abnormal patterns obtained in cases of dementia paralytica and in those of tabes. Furthermore, if the cortical lesions in dementia paralytica were solely responsible for the abnormal electrical potentials, asymmetric disturbances should be obtained from homologous areas in many cases. There is, however, no distinguishing difference in the character of the patterns, and the majority of records in cases of dementia paralytica, as well as in those of all other forms of neurosyphilis, show symmetric patterns from homologous areas of the two hemispheres (fig. 6). This symmetry persists also during the modification of the records which occurs during treatment. It seems necessary to postulate a central focal lesion in the base of the brain (mesencephalon; diencephalon) to explain these observations.

In the majority of records obtained in cases of all types of neurosyphilis the abnormal activity is obtained predominantly from the frontal and precentral regions. In dementia paralytica the cortical lesions are usually most marked in the frontal regions. The significance of this location of the lesions in this disease in relation to the electroencephalograms is probably of no importance because abnormal activity occurs predominantly in the frontal parts of the cerebrum not only in dementia paralytica but in other types of neurosyphilis. This predominance of abnormal activity in the frontal regions is also a striking characteristic in some records in cases of

other neuropsychiatric disorders, such as epilepsy, encephalitis, schizophrenia, manic-depressive disorders and agitated depressions. Of the 124 cases in which the disease was classified as dementia paralytica, 38 were of the tabetic type, the diagnosis being based on the presence of mental symptoms in addition to the classic signs of tabes. In 85 per cent of these cases there were borderline and abnormal records. There is, therefore, no significant difference in the percentage of borderline and abnormal rec-



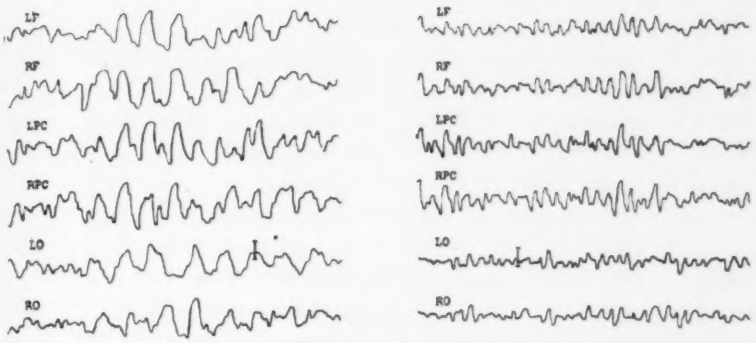


Fig. 6.—Six simultaneous recordings from the left and right frontal, the left and right precentral and the left and right occipital regions in 3 cases of neurosyphilis, illustrating the similarity of the patterns from homologous areas of the two hemispheres. The upper tracing illustrates two patterns in a case of juvenile dementia paralytica obtained before and after treatment. Although in the tracings before treatment the patterns from the frontal, precentral and occipital regions are different, the patterns from two homologous points (e. g., left and right occipital) are similar. The tracings taken on April 1 were obtained after treatment and illustrate that the similarity of patterns from homologous areas has been retained. The lower left hand tracing shows a very abnormal pattern of slow activity, again illustrating the similarity of the abnormal activities from homologous areas. The lower right hand tracing is a more normal pattern, again showing the similarity of the tracings from homologous areas. The significance of this observation is discussed in the text.

ords in cases in which the combined clinical picture of tabes and dementia paralytica was present and in cases either of pure tabes or of dementia paralytica. This fact indicates that the combined lesions of the midbrain and cortex (tabetic form of dementia paralytica) result in no more severe disturbance of the cortical rhythm than the lesions of pure tabes, which are primarily in the brain stem, and if present in the cortex are minimal. That the lesions in the region of the midbrain are of importance in the consideration of the significance of the electroencephalogram in neurosyphilis is emphasized by the fact that this is the most commonly affected region of the central nervous system in all forms of the disease. We are obliged, therefore, to consider the possibility of cortical dysrhythmia in neurosyphilis having its point of origin outside the cortex, although in dementia paralytica the cortical lesions probably have some effect. Earlier workers in the field of electroencephalography, notably Adrian, Bishop, Davis, Hoagland and Jasper,[4] have suggested that there may be a "pacemaker" within the central nervous system which regulates the frequency of the cortical rhythm. The electroencephalographic pattern is altered during physiologic sleep. The region of the brain primarily responsible for the regulation of the sleep-wake rhythm has been shown by Ranson to lie in the hypothalamus. This fact, together with the disturbance of the cortical electrical patterns by tumors in the third ventricle and in the diencephalon, demonstrates the importance of this general region of the brain in the regulation of cortical electrical potentials.

Studies by Dusser de Barenne and McCulloch [5] and by Morrison and Dempsey [6] on animals show that the normal frequency pattern from the cortex can be altered by lesions in certain parts of the diencephalon. This line of reasoning is presented as a working hypothesis in an attempt to reach a deeper understanding of the neurophysiologic significance of electrical brain potentials from clinical material.

In the interpretation of electroencephalographic tracings it is of practical importance to determine the significance of the various types of abnormal activity. The records obtained in our cases of neurosyphilis show that slow activity may be more significant pathologically than rapid activity. Most of the records showing slow activity which returned to normal during treatment passed through a stage in which rapid activity predominated. Similar alterations have been observed by us in the records of patients with psychoses due to drug intoxication. Records taken when the patient is stuporous and confused show slow, high voltage activity. Later, when mental clearing occurs, rapid activity appears

4. Adrian, E. D.; Bishop, G. H.; Davis, H.; Hoagland, H., and Jasper, H. H.: Excitation Phenomena, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1936, vol. 4.

5. Dusser de Barenne, J. G., and McCulloch, W. S.: The Direct Functional Interrelation of Sensory Cortex and Optic Thalamus, J. Neurophysiol. **1**:176, 1938.

6. Personal communication to the authors.

before the normal pattern is reestablished. Slow, high voltage activity, although indicating a severe alteration in cerebral function, is not necessarily irreversible (fig. 5; samples *A*, *B* and *F*). This has been frequently observed by others and is well demonstrated in a case of encephalitis reported by Lindsley and Cutts [7] in which slow activity gradually disappeared with clinical improvement. In our experience slow activity is more commonly seen in the records of patients with epilepsy, brain tumor, cerebrovascular lesions, encephalitis and other neurologic disorders. Rapid activity is more commonly seen in the records of patients with schizophrenia,[8] affective disorders [9] and other psychiatric conditions.[2] As a rule, slow activity was found in patients with dementia paralytica exhibiting confusion, disorientation and loss of memory, while rapid activity was most frequently present in those showing disturbances in mood, delusions and hallucinations.

SUMMARY AND CONCLUSIONS

1. Electroencephalographic records were obtained from 175 patients with neurosyphilis, in 124 of whom the condition was diagnosed as dementia paralytica, in 20 as tabes dorsalis, in 11 as juvenile dementia paralytica, in 8 as optic nerve atrophy and in 12 as meningovascular neurosyphilis. These tracings are compared with the records from 215 normal controls.

2. Normal electroencephalographic tracings were found for 19 per cent of the patients (treated and untreated) and for 70 per cent of the controls. Borderline records were found for 28 per cent of the patients and for 23 per cent of the controls. Abnormal records were found for 53 per cent of the patients and for 7 per cent of the controls.

3. Abnormal electroencephalographic tracings were as common among patients with pure tabes and those with optic nerve atrophy as among patients with dementia paralytica.

4. The records of 73 untreated patients with dementia paralytica showed a higher percentage of borderline and abnormal patterns than the records of 63 patients who had received treatment for nine months or more.

5. No characteristic electroencephalographic pattern was found to be associated with neurosyphilis or with any type of neurosyphilis. The electroencephalogram has therefore no significant diagnostic value.

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7. Lindsley, D. B., and Cutts, K. K.: Clinical and Electroencephalographic Changes in Child During Recovery from Encephalitis, Arch. Neurol. & Psychiat. **45**:156-161 (Jan.) 1941.

8. Gibbs, F. A.: Cortical Frequency Spectra of Schizophrenic, Epileptic and Normal Individuals, Tr. Am. Neurol. A. **65**:141, 1939. Finley and Campbell.[2]

9. Davis, P. A.: The Electroencephalograms of Manic-Depressive Patients, Am. J. Psychiat. **98**:430-433, 1941. Finley and Campbell.[2]

6. The 73 untreated patients with dementia paralytica presented a degree of abnormality in the electroencephalogram which corresponded roughly with the clinical severity of the disease.

7. Follow-up electroencephalographic records on many of the patients undergoing treatment with clinical improvement are presented. In most instances there was concurrent improvement in the electroencephalographic tracings.

8. Electroencephalograms with abnormally slow, high voltage cycles were more likely to be found among patients with dementia paralytica who showed confusion, disorientation and profound memory loss, while rapid cycles were more common among those with euphoria or other mood disturbances and paranoid ideas without the aforementioned signs. Slow cycles indicated more serious cerebral dysfunction than did rapid cycles.

9. The majority of abnormal patterns associated with all types of neurosyphilis were similar from homologous areas of the two hemispheres. This observation, together with the fact that abnormal records were as frequent in cases of pure tabes and optic nerve atrophy, suggests that lesions in or near the upper portion of the midbrain and the diencephalon may have more to do with the abnormal cortical electrical potentials than the cortical lesions.

DISCUSSION

DR. LEON H. CORNWALL, New York: I wish to compliment the authors on their presentation of the most extensive contribution to the subject of electroencephalography in relation to neurosyphilis that has been made. Dr. Hoefer has made available to me his data pertaining to neurosyphilis, consisting of the records of 22 cases, in 9 of which the diagnosis was meningovascular syphilis, in 7 parenchymatous and in 6 congenital.

Obviously, the number is too small to have statistical value. Some of the results were a bit astonishing, but I find that they are in accord with the larger experience of Drs. Finley, Solomon and Rose. Among the records that I have reviewed were those of 4 patients with dementia paralytica; 2 of these gave electroencephalographic patterns regarded as normal. These patients have been under my observation for seven and nine years, respectively. Both were given fever therapy, followed by intensive arsenical and other medication. They are both still slightly euphoric and lacking in normal insight and manifest defects of memory and judgment. They are, however, in excellent physical condition and represent social recoveries. The normal graph in 2 of the 4 cases of dementia paralytica is comparable to the normal patterns reported by Dr. Finley in 10 of 18 cases after prolonged treatment. In these 10 cases the serologic reactions of the blood and spinal fluid were also negative.

The authors found borderline or abnormal patterns in 81 per cent of their 175 cases. In our 22 cases there were abnormal or borderline patterns in 60 per cent. I suspect that most of our patients had received more treatment before the electroencephalograms were made than had those reported by Dr. Finley.

Of the authors' 73 patients with untreated or inadequately treated syphilis, 88 per cent gave abnormal patterns. In their group that received treatment for nine months or slightly longer (63), the incidence of abnormal patterns was reduced to 73 per cent, and in the serologically negative patients just referred to (18) the incidence of abnormal patterns was 55 per cent. It seems to me that this justifies the conclusion that there is some correlation between the degree of abnormality of the pattern and the clinical severity or, perhaps better, the acuity of the neurosyphilitic lesions.

The absence of a distinguishing difference between the character of the patterns in dementia paralytica and that in tabes dorsalis is an important observation in view of the difference in the topographic localization of the essential neuropathologic lesions, as the authors have pointed out in their paper. In my series there were 4 cases of optic nerve atrophy, and in all of them the patterns were abnormal. In 1 of these cases the greatest abnormality was in the record from the occipital area. In my opinion, the results in the cases of tabes dorsalis give substantiation to the hypothesis that cortical rhythm may be regulated by some of the deeply situated structures in the hypothalamus, as suggested by the authors, or in the thalamus, as indicated by the work of Morrison and Dempsey. Because of the age, phylogenetically considered, of the diencephalic and mesencephalic structures and their exercise of functions for so many millenniums before telencephalization, it seems highly probable that these structures may modify or influence cortical activity and therefore exert an effect on cortical rhythms.

Dr. Frederic A. Gibbs, Boston: The authors are to be congratulated on this study, which I believe will stand for a long time as the authoritative and definitive statement of what is encountered in the electroencephalogram in neurosyphilis. When electroencephalographic studies were first begun in clinical cases, there was a good deal of talk about the likelihood that the electrical activity of the cortex was an epiphenomenon, something rather distantly related to the actual goings-on in the cortex. It is possible, however, for epiphenomena of various sorts to be useful.

Even though in the electroencephalogram one is not studying the actual neurologic goings-on in the cortex, if these phenomena are sufficiently carefully studied by men who are aware of the neuroanatomic, histologic and psychiatric components of the problem, the electroencephalographic technic can without doubt be made useful. The authors conclude that because of the nonspecificity of the abnormalities encountered they do not see how the technic could be used for diagnostic purposes. This, it seems to me, is a warranted conclusion, but they conclude also that the technic can be used for investigative purposes in cases of syphilis of the central nervous system. It seems to me that that is the highest use which a technic can serve. One of the most extraordinary things reported in the present paper is the observation that there is as much abnormality in tabes as there is in dementia paralytica. If the authors are able to continue these investigations and find out why abnormalities appear in the cortex in tabes, they will have resolved one of the important problems of electroencephalography, for it is true that abnormalities in the electroencephalogram do not correlate absolutely with psychic disorder or with other evidence of brain dysfunction. Why there is not a one to one relation between the electrical activity of the cortex and psychic activity is a major problem. I know that Dr. Finley has already embarked on a study of the cortical disorder produced by deep lesions in order to gain insight into this matter.

Dr. A. E. Bennett, Omaha: Within the past year, my associate, Dr. Paul T. Cash, and I have instituted the electroencephalographic procedure as a routine in

the study of all patients with dementia paralytica treated in the University of Nebraska fever therapy research department. During this time we have examined 10 consecutive patients who failed to obtain a remission with combined induction of artificial fever and chemotherapy. Some of these had previously had treatment with malaria. Of this series, 9 showed definitely abnormal records all characterized by extremely low voltage and marked disturbance of the alpha activity, which was irregular in appearance and of low incidence. There were an increased incidence of fast activity in all leads and only occasional slow potentials.

Eighty to 90 per cent of the patients with an acute process before treatment had records of moderate amplitude with marked disturbance of all rhythmic activity and the appearance of fast activity in all leads and frequent slow potentials. In the majority the area of greatest involvement was in the frontal regions and was usually more marked on one side than on the other. In the remaining cases of the acute stage the record was normal. In 1 of these a less regular-appearing record followed treatment, even though there was clinical improvement.

In all cases in which the record was abnormal before treatment, after fifty hours of fever treatment and chemotherapy, a definite increase in amplitude, with a return of synchronous rhythmic activity, increase of fast activity in the frontal and motor leads and "good" alpha activity from the occipital leads occurred. In all the slow potentials disappeared.

The slow potentials would seem to be a gross measure of the severity in the cases of an acute process, and in a rather high percentage they are indicative of an acute process without actual destruction of tissue, for the electrocortical functions return to normal after treatment.

The amplitude and the incidence of rhythmic activity would also seem to be a gross measure of the duration of the process. There is moderate depression of amplitude and decreased rhythmic activity in the cases of an acute process. In the cases of advanced disease in which treatment failed there is extremely low voltage with nearly complete or complete absence of alpha activity.

Why in some of the cases of treatment failure and in some of the cases of acute disease the records are normal is difficult to explain in the present stage of knowledge of electrocortical function. I should like to learn whether Dr. Finley has any explanation for these discrepancies.

Dr. Knox H. Finley, Boston: With regard to Dr. Bennett's question, there were many exceptions to the results in this preliminary study, and these exceptions raise many interesting and difficult problems, which Dr. Bennett will appreciate. Rather than attempt to answer them from our preliminary data, we prefer to withhold comment until we have had the opportunity to follow our present material for a longer period.

MIXED TUMORS OF THE SPINAL CANAL

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AND
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MINNEAPOLIS

It is possible to differentiate mixed tumors from other lesions of the spinal canal by the typical clinical history and the characteristic roentgenologic evidence. It is by the early recognition and treatment of these tumors that good results by surgical removal are obtained.

Mixed tumors of the spinal canal are uncommon. In 1883 Chiari [1] reported the first case of an epidermoid tumor. In 1931 Hosoi [2] collected 10 cases of teratoid tumors occurring since 1883. Gross in 1934 [3] collected 19 cases of dermoid and epidermoid tumors from the literature, to which he added 1 case. In 1938 Bradford [4] brought the literature up to date by collecting 9 cases of dermoid or epidermoid cysts of the spinal canal reported since 1934.

Mixed tumors are now accepted as arising from embryonic rests.[5] At the stage of embryonic development at which the neurectoderm is separated from the medullary plate, inclusions of epidermal cells may occur. These inclusion cells possess potentialities for growth and differentiation; the age of embryonic life at which the inclusion occurs determines the position and structure of the resulting tumor.[6] An inclusion in early embryonic life causes the isolation of multipotential ectodermal

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From the Division of Neurosurgery of the Department of Surgery, University of Minnesota Hospitals.

The researches presented here were supported by grants of the Graduate School of the University of Minnesota.

1. Chiari, H.: Centrales Cholesteatoma des Dorsalmarkes mit vollkommen entwickelter auf- und absteigender Degeneration, Prag. med. Wchnschr. **8**:378, 1883.

2. Hosoi, K.: Intradural Teratoid Tumors of the Spinal Cord, Arch. Path. **11**:875 (June) 1931.

3. Gross, S. W.: Concerning Intraspinal Dermoids and Epidermoids, J. Nerv. & Ment. Dis. **80**:274, 1934.

4. Bradford, F. K.: Intramedullary Dermoid Cyst, Ann. Surg. **107**:107, 1938.

5. Ewing, J.: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1919, p. 931. Bostroem, E.: Ueber die pialen Dermoid, Epidermoid und Lipom und duralen Dermoide, Centralbl. f. allg. Path. u. path. Anat. **8**:1, 1897.

6. Torak, J., cited by Salotti, A.: Dermoide del midollo spinale, Arch. ital. di chir. **19**:135, 1927.

cells that are capable of forming hair and glandular appendages. Inclusions at a later date involve cells which have already become differentiated, and so development is limited to simple squamous epithelium.

Mixed tumors may be classified into three types depending on the number of germ layers present.[7] Teratomas are those complex structures composed of tissues and organs representing all three germ layers; dermoids contain tissue of mesodermal and epithelial origin, and epidermoids contain tissues of epithelial origin but lack definite dermal structures.

Since mixed tumors of the spinal canal are relatively uncommon and since they present a rather typical clinical picture as well as roentgenologic evidence, we are presenting 3 proved cases occurring at the University of Minnesota Hospitals since February 1939.

REPORT OF CASES

CASE 1.—V. R., a man aged 36, the father of two children (3 and 2 years old), gave a history of marked thoracic kyphosis and dimpling of the skin over the sacrum since birth. At the age of 13 years he was admitted to an orthopedic hospital. At that time the positive findings were paresis and atrophy of the lower extremities, difficulty in controlling urine, thoracic kyphosis and dimpling of the skin over the sacrum. A back brace was applied and worn for three years, without relief, although the symptoms did not progress. At the age of 33 years, or 3 years before the present admission, the patient first noted recurrent spasmodic pains in his back and down his legs, increasing difficulty in walking due to spasticity of his legs, diminished ability to control urine and feces and decrease in sexual potency. However, he was able to continue his work as a common laborer. He was admitted to the University Hospitals on Feb. 26, 1939, when 36 years old.

Physical Examination.—Examination on admission revealed thoracic kyphosis and a fistulous opening over the sacrum, with hair growing from and about it. There were paresis of the lower extremities, atrophy of both legs, especially the right, with shortening of the achilles tendon, hypoactive knee jerks, absence of ankle jerks and decreased sensation over the second to the fifth sacral segments. Roentgenograms (fig. 1) of the lumbar portion of the spine and the sacrum demonstrated a large dilatation of the spinal canal, chiefly at the levels of the third, fourth and fifth lumbar vertebrae. The pedicles of the third and fourth lumbar vertebrae were so much decalcified and eroded that they could scarcely be made out in the roentgenograms. The interpedicular distances, which greatly exceeded the normal limits (fig. 8), were approximately as follows:

	Mm.
Thoracic 11	19.5
Thoracic 12	23.0
Lumbar 1	25.0
Lumbar 2	27.0
Lumbar 3	37.0
Lumbar 4	50.0
Lumbar 5	40.0

7. Baker, A. B.: An Outline of Neuropathology, Minneapolis, University of Minnesota Press, 1940, p. 23.

The greatest anteroposterior diameter of the canal was 57 mm., at the level of the fourth lumbar vertebra. The pedicles of the third and fourth lumbar vertebrae were much flattened and eroded when viewed anteroposteriorly, and they were extremely elongated in the lateral roentgenograms. There were lordosis and slight scoliosis of the lumbar portion of the spine. There was definite narrowing of the intervertebral disks between the third and the fourth and the fourth and the fifth lumbar vertebrae. A rounded, cystic area of erosion extended directly into the body of the fourth lumbar vertebra, almost to its anterior margin. This area measured 2.5 cm. in diameter. There was complete lack of fusion of the laminas of the sacrum. These changes were interpreted as due to a large, slowly growing, expanding lesion within the spinal canal, situated chiefly at the levels of the third, fourth and fifth lumbar vertebrae.

A diagnosis of tumor of the spinal cord having been made, operation was performed on March 2, 1939.

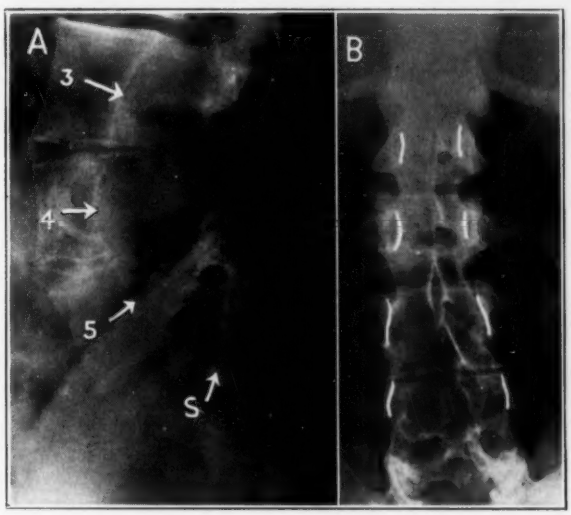

Fig. 1 (case 1).—Roentgenograms of the lumbar portion of the spine. In these and in subsequent roentgenograms arrows point to posterior surfaces of vertebral bodies and lines indicate inner borders of pedicles of vertebrae. *A*, lateral view, showing erosion of posterior surfaces of bodies. The fusiform enlargement of the spinal canal is evident. *B*, anteroposterior view, showing erosion of inner borders of pedicles.

Operative Procedure.—A laminectomy of the third, fourth and fifth lumbar vertebrae was performed. A fibrous tumor mass was exposed. It was connected with the dimple in the skin. Associated with this fibrous mass were two cysts containing mucoid material. One of these cysts was approximately 1 cm. in diameter and was within the fibrous mass. The other was on the surface of the fibrous mass and was 4 inches (10 cm.) in length and 1½ to 2 inches (3.8 to 5 cm.) in diameter. The tumor had caused pressure erosion of the bodies of the vertebrae and seemed to have replaced the filum terminale. Its position was such as to spread the rootlets of the cauda equina, and they were situated on the entire surface of the tumor, some of them embedded in the walls of the larger cyst.

The fibrous mass was removed. The cysts were evacuated, but the fibrous wall of the large cyst was not completely removed because the rootlets were so embedded in it that they could not be preserved if this were done. The dura was closed.

Pathologic Report.—Microscopic sections revealed a varied group of elements, including adult fat cells, myxomatous tissue, embryonic and adult cartilage, fibrous tissue, glial cells, glandular tissue with goblet cells and squamous epithelium.

Diagnosis.—The diagnosis was teratoma (fig. 2).

Postoperative Course.—After the operation the patient's general condition gradually improved. Neurologic examination on discharge from the hospital revealed that the knee and ankle jerks were active and equal on the two sides; there was no Babinski sign or clonus, and sensation was intact except over the third to

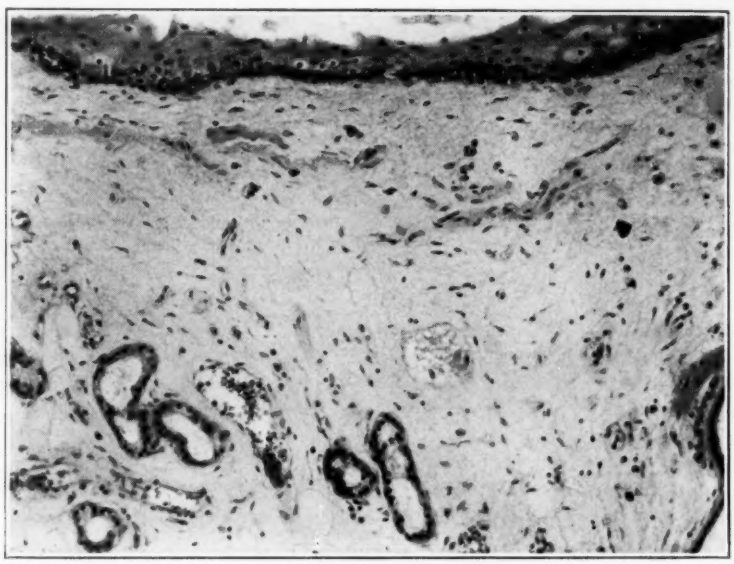

Fig. 2 (case 1).—Photomicrograph of teratoma.

the fifth sacral segments. There was spastic paresis of the lower extremities, although muscle strength was increased over the preoperative state. The patient had obtained partial control of the bladder and rectum.

After discharge the patient continued to improve until September 1939, seven months after operation, at which time pain in his back again developed. This was soon followed by incontinence of urine and feces. He was readmitted to the hospital on Sept. 22, 1939. Neurologic examination revealed that the knee jerk was diminished on the right and normal on the left and the ankle jerks were absent bilaterally. Sensation was diminished over the fourth lumbar to the fifth sacral segments, and the strength of the leg muscles was diminished as compared with that in the previous examination. It was the impression at this time that the patient had compression of the cord as a result of refilling of the cysts or growth of the teratomatous elements. He became progressively worse. He was last examined on Jan. 14, 1941, at which time there were spastic contractures of his

lower extremities, incontinence of the bowel and bladder, diminished knee and ankle jerks bilaterally and analgesia over the fourth lumbar to the fifth sacral nerve segment.

This patient presented symptoms over a period of twenty-five years. The slow-growing character of a mixed tumor was evident. Operation was unsuccessful, owing to recurrence of an incompletely removed tumor. True teratomas of the spinal cord are extremely rare. There are reported in the literature only 2 other cases.[8]

Case 2.—A. L., a boy aged 7, had, according to his mother, developed normally until 13 months of age. At that time she noted the child was unable to straighten

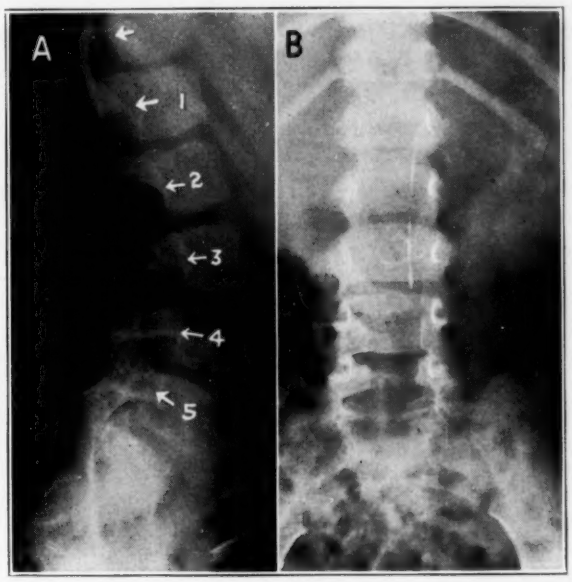

Fig. 3 (case 2).—Roentgenograms of the lumbar portion of the spine of a patient with a teratoma. *A*, lateral view; *B*, anteroposterior view.

his hips and that if he was placed on his back he would cry and scream until turned onto his side or abdomen. On examination at a local hospital, positive physical findings included an area of hypertrichosis over the lower lumbar portion of the spine, spina bifida, as demonstrated roentgenographically, atrophy and spasticity of his lower extremities and absence of knee and ankle jerks. There were no sensory changes. Traction was applied to the lower extremities for four months. The child improved and was able to be up and about until he was 3½ years of age, at which time there developed a peculiar gait and severe pains in both legs. Traction on his legs was again applied, but he obtained no improvement. At this time examination revealed that when the child walked he swung

8. Walker, A. A., and Moore, C. H.: Tumors of the Spinal Cord in Children, Am. J. Dis. Child. **57**:900 (April) 1939.

from the metatarsals of one foot to those of the other, holding his spine rigid. On bending over he held his spine rigid and obtained flexion at the hips only. The clinical impression at this time was "spina bifida with meningocele adhesions, causing root pain." Laminectomy was performed, and "a heavy cartilaginous band was removed from the center of the bulging dural sac." The child's convalescence was normal, and he was free of complaints until the age of 6, when he again began to have severe spasmodic pains in his back and legs. He refused to eat and lost considerable weight. He was then (Dec. 3, 1940) admitted to the University Hospitals.

Physical Examination.—Examination revealed an undernourished boy with definite contractures of the hamstring muscles of both legs, the right being worse than the left. The knee and ankle jerks were absent; there were no sensory changes. Roentgenograms of the lower thoracic and lumbar portions of the spine (fig. 3) revealed a diffuse fusiform enlargement of the entire lumbar part of the canal. The enlargement was greatest at the level of the second and third lumbar vertebrae. The greatest anteroposterior diameter of the canal was 45 mm. The interpedicular measurements were as follows:

	Mm.
Thoracic 10	19.0
Thoracic 11	20.5
Thoracic 12	23.0
Lumbar 1	27.5
Lumbar 2	33.0
Lumbar 3	35.0
Lumbar 4	33.5
Lumbar 5	32.0

These measurements exceed the normal range for his age group (fig. 9).

There was perhaps slightly increased lordosis of the lumbar portion of the spine. The laminas were very thin and difficult to make out in the region of the second and third lumbar vertebrae. There was evidence of an old hemilaminectomy of the left side of the third, fourth and fifth lumbar vertebrae. The pedicles of the upper lumbar vertebrae, especially the second and third, in addition to being separated, were much flattened and eroded on their inner borders. The findings were considered to be consistent with the presence of a slowly growing, but large, expanding tumor within the lumbar part of the spinal canal. The growth was thought to be a simple cyst, an epidermoid or a lipoma.

Because of the clinical and roentgenologic impression that the patient had a tumor of the spinal cord, laminectomy was performed on Dec. 18, 1940.

Operative Procedure.—The spinal cord was first exposed in the midlumbar region by removing three laminas. The laminas were very thin and ribbon-like, so that when the muscles were scraped from the dorsal surface of the laminas they bent with slight pressure. An intradural cyst was observed to fill completely the spinal canal at this level. The laminas were eventually removed cephalad up to and including those of the eighth thoracic vertebra and caudad to the former laminectomy, which extended to the upper portion of the sacrum. The greatest circumference of the cyst was in the midlumbar region. It was opened on the dorsal surface and the contents, 2½ ounces (70.9 Gm.) of a greenish brown liquid, were removed. The sac was then dissected free from the dura. On the anterior surface of the sac were rootlets of the cauda equina; some were

adherent to the external surface of the sac. The sac extended from the eighth thoracic vertebra to the upper end of the sacrum. The sac was completely removed, but a strand of tissue, closely associated with the dura on the dorsal surface of the cord, continued even cephalad to the exposed area. At the upper end of the exposure this strand of tissue was clipped with a silver clip and cut across. At its lower end the sac was attenuated and easily removed. The dura was closed.

Pathologic Report.—Microscopic examination revealed a cavity lined by a transitional type of stratified epithelium, which contained small papillary folds. The outer layer was composed of connective tissue. Islands of cartilage, adipose tissue and glandular acini that were forming mucin were observed in the wall of the cyst. A few scattered nerve fibers were also seen in the wall. The diagnosis was teratoma (fig. 4).

Fig. 4 (case 2).—Photomicrograph of teratoma.

Immediately after operation the patient was incontinent of urine and feces. He was treated with Bellis'[9] modification of Monro's tidal bladder irrigation. After three weeks he acquired control of both bladder and rectum. Strength in the lower extremities gradually increased, and by the sixth postoperative week he was able to walk without the aid of crutches. A Taylor back brace was fitted, and he was discharged from the hospital. Since then he has become progressively more active. He was last seen in the outpatient department on April 15, 1941, four months after operation, at which time there was no motor or sensory paralysis or pain, but the deep reflexes in the lower extremities were still hypoactive. He was continent of feces and urine.

9. Bellis, C. J.: An Improved Apparatus for Tidal Drainage of the Urinary Bladder and Empyema Cavities, Surgery **8**:791, 1940.

In this case, the symptoms that began at the age of 13 months were undoubtedly due to the teratoma. The laminectomy performed at the age of 3½ years, at which time "a heavy cartilaginous band" was said to have been removed, acted as a decompression of the cord and permitted alleviation of the symptoms for two and a half years. However, the tumor at the age of 6 years had grown sufficiently to cause compression of the cord and to give rise to symptoms. The excellent return of function was probably due to the minimal injury of the lower portion of the cord and nerve roots by the soft caseous-like contents of the sac.

Case 3.—M. S., who was born on Oct. 21, 1936, was admitted to the University Hospitals on Jan. 8, 1937 with a diagnosis of pneumonia. At that time a

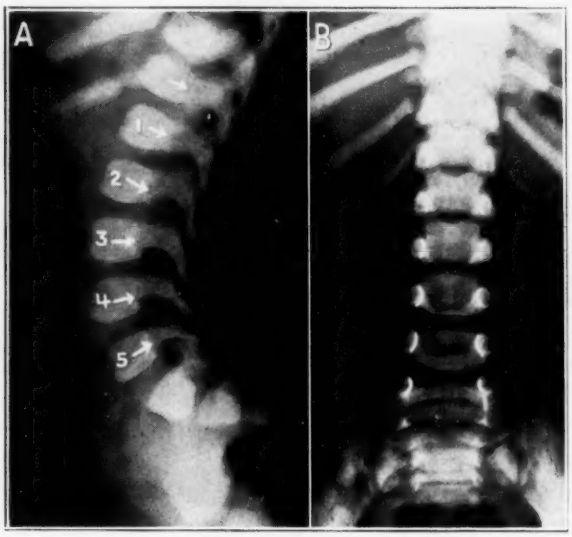

Fig. 5 (case 3).—Roentgenograms of the lumbar portion of the spine. *A*, lateral view; *B*, anteroposterior view.

small dimple was noted over the sacrum, and the child was thought to have spina bifida occulta. No other abnormalities were found.

On June 27, 1938 the patient was readmitted with symptoms of increasing irritability, restlessness and nausea and vomiting, which had developed after a minimal injury to the head two days previously. At that time the mother stated that the child slept on her side or abdomen and cried if turned on her back and that she walked in a lordotic position and did not control her feet very well. During the first month in the hospital the patient had intermittent bouts of fever, was irritable and showed signs of meningeal irritation (stiff neck; positive Kernig sign). A diagnosis of meningitis was made. Repeated spinal punctures were performed. The cerebrospinal fluid contained from 1,100 to 3,100 cells per cubic millimeter, with 70 to 80 per cent polymorphonuclears; however, no definitely predominant organism was cultured. Sulfanilamide was given, and signs of meningeal

irritation partially disappeared. A spinal puncture was performed on Aug. 21, 1938 and pure pus was obtained. It was thought that an external abscess had developed; so a laminectomy was performed at the third lumbar vertebral level and 5 cc. of pus was found in the subdural space in a very thin-walled sac situated between the rootlets of the cauda equina. This was evacuated. The patient's postoperative convalescence was uneventful except that a persistent draining sinus was formed at the lower end of the sac. The possibility of osteomyelitis was entertained, and roentgenograms of the lumbar portion of the spine were made (fig. 5). They showed a generalized increase in the width of the spinal canal over the entire lumbar area and probably in the lower thoracic region. The interpedicular measurements were as follows:

	Mm.
Thoracic 10	16.5
Thoracic 11	18.0
Thoracic 12	19.0
Lumbar 1	19.5
Lumbar 2	20.5
Lumbar 3	20.5
Lumbar 4	22.0
Lumbar 5	26.0
Sacral 1	27.5

Although these measurements do not greatly exceed the normal range (fig. 10), the increase of 4 mm. in the interpedicular distances between the fourth and the fifth lumbar vertebra is probably significant. In the anteroposterior view the greatest diameter of the lumbar portion of the canal measured about 20 mm. These findings were consistent with a generalized increase in the lumbar part of the spinal canal. There was a congenital defect, or spina bifida, of the laminas of the first and second sacral segments.

The true significance of the enlargement of the lumbar portion of the spinal canal was not recognized, so that the patient was discharged from the hospital.

The patient was readmitted on May 23, 1939 with a history of episodes of fever, irritability, loss of sphincter control and weakness of the legs. Examination revealed paresis of the lower extremities, foot drop on the left and hyperactive knee and ankle jerks. A diagnosis of recurrence of the abscess and possible osteomyelitis of the vertebra was made. On June 2, 1939 the second operation was performed, at which time the old sinus tract was dissected into the dural sac and an abscess found. Five to 6 cc. of pus was removed. Convalescence after operation was uneventful except that pus continued to drain from the site of the laminectomy.

On Dec. 12, 1939 the patient was readmitted with a history of having a persistent sinus at the site of the former operation. There was partial paralysis of the bladder, with dribbling of urine. On examination an occasional flake of cholesterol-like material was seen in the pus coming from the sinus. Reflexes in the lower extremities were hyperactive at this time. The sinus tract was explored for the third time, and cholesterol-like material surrounded by fibrous tissue was observed. Biopsy of this tissue revealed squamous epithelium. The lesion was now recognized as an infected epidermoid cyst. The patient improved; so she was discharged from the hospital and followed in the outpatient department.

On May 1, 1940 flaccid paralysis of the lower extremities and incontinence of urine and feces suddenly developed. The child was hyperirritable and cried a great deal at night, especially when placed on her back. The infected cyst was again incised, and "thick greenish pus, containing flakes of cholesterol-like material" was obtained. No attempt was made to remove the cyst on account of the acute stage of the infection.

On July 15, 1940, when all signs of acute inflammation had subsided, the fifth operation was performed.

Operative Procedure.—The dimple over the first sacral vertebra was excised, and a tract leading from this was followed down into the sacral part of the spinal canal, where it communicated with a large sac containing cholesterol crystals. The laminectomy was extended and the sac dissected upward until finally it was traced

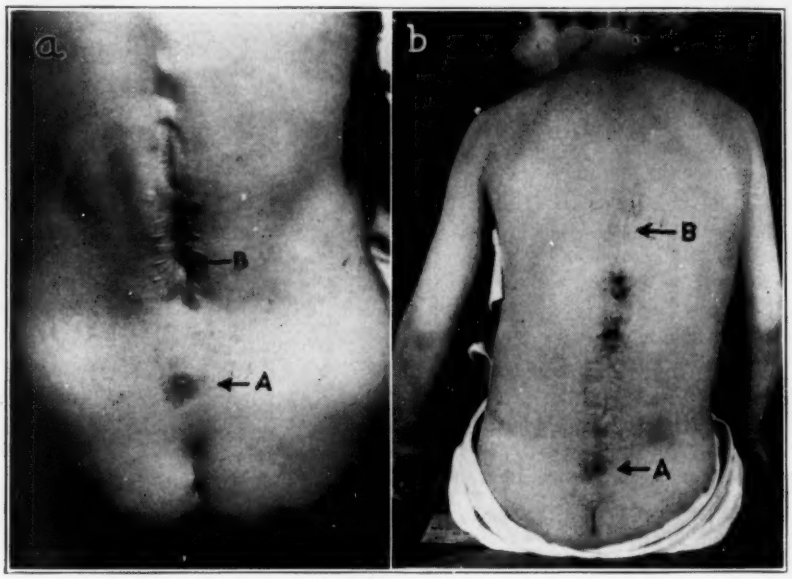

Fig. 6 (case 3).—(*a*) Photograph before final operation for removal of epidermoid cyst. *A*, dermoid sinus; *B*, draining sinus. (*b*) Photograph after final surgical removal of epidermoid cyst to show length, *A* to *B* of laminectomy.

to the site of the draining sinus, which was over the lower thoracic portion of the spine. The dissection was continued still farther upward, to a point 1 to 2 cm. above the draining sinus, and the sac removed up to this point. The laminectomy at the conclusion of the operation extended from the twelfth thoracic to the first sacral vertebra, but still a portion of the epidermoid cyst or tract extended beyond the upper end of the exposure (fig. 6 *A* and *B*).

Pathologic Report.—The gross specimen consisted of 12 cm. of stringlike tissue, which was beaded at several points by shiny cystic nodules, the largest being 1.5 cm. in diameter. When opened they were seen to be filled with sebaceous-like material. Microscopic examination showed the inner surface to be squamous epithelium that was cornified on its inner surface. This epithelial lining was sur-

rounded by hyaline connective tissue. There was a diffuse inflammatory exudate of plasma cells and neutrophils. The diagnosis was infected epidermoid cyst (fig. 7).

After operation, the patient gradually gained continence of urine and feces and her legs became stronger. When last seen, on Nov. 28, 1940, she could walk without support. A draining sinus was still present at the cephalad end of the laminectomy wound.

This lesion was thought to be an abscess, but cholesterol plaques, which were present even at the first operation, should have suggested an infected dermoid or epidermoid cyst. Apparently, the epidermoid sac became infected secondary to the meningitis, as a result of traumatization of the cyst wall or actual puncturing of the cyst with the spinal

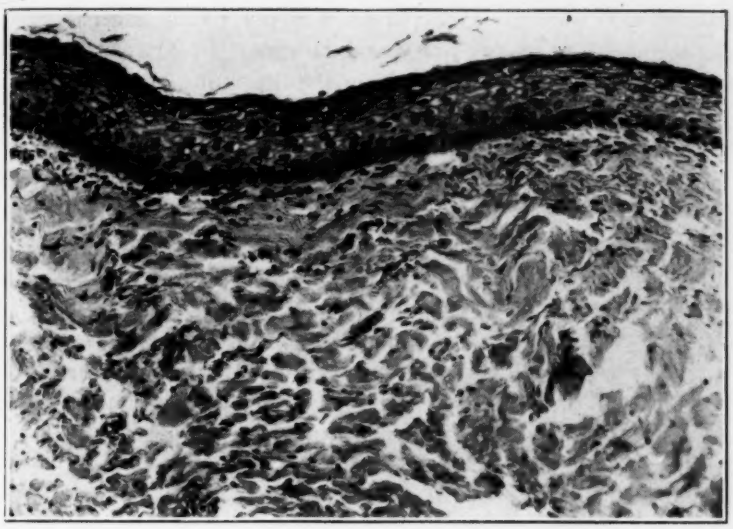

Fig. 7 (case 3).—Photomicrograph of epidermoid cyst.

puncture needle. Continued drainage is due to the cephalad continuation of the cyst beyond the laminectomy wound. Removal of the remaining portion of the epidermoid sac may be necessary if symptoms recur.

COMMENT

Several authors [10] have observed that patients with tumor of the spinal cord have pain along the spine when lying on the back and that this pain is relieved only when the patient sits or stands. In 2 of our patients the pain that occurred when they were placed on the back was

10. (*a*) Naffziger, H. C., and Jones, O. W., Jr.: Dermoid Tumors in Spinal Cord, Arch. Neurol. & Psychiat. **33**:941 (May) 1935. (*b*) Masson, C. B.: Dermoid of the Spinal Cord, ibid. **40**:554 (Sept.) 1938. (*c*) Walker and Moore.[8]

relieved when they were placed on the side or abdomen. Traction on the sensory roots or irritation of the sensitive inner layer of the dura [10b] is relieved by this change in position.

All 3 of our patients had associated spina bifida, which is consistent with the congenital origin of mixed tumors from embryonic rests.

Two features are present in these patients that are characteristic of mixed tumors of the spinal canal: first, the long duration of symptoms, with slow progression; second, the characteristic roentgenologic evidence. These two features are characteristic, but not diagnostic, of mixed tumors, for lipoma gives the same chronicity of symptoms and produces similar roentgenologic changes.[11]

The symptoms in all of these patients began in early childhood and progressed very slowly. One patient was not totally incapacitated in spite of symptoms of twenty-five years' duration. In 20 cases of dermoid and epidermoid tumors collected from the literature, Gross [3] found the average duration of symptoms to be ten years and the average age at time of operation to be the third and fourth decades. This delayed appearance of neurologic signs and symptoms is best explained by the slow growth and the soft content of these tumors.

The roentgenologic appearance of mixed tumors of the spinal canal is characteristic. Pressure erosion may occur in the case of any benign intraspinal tumor, but mixed tumors are characterized by a diffuse fusiform enlargement of the spinal canal that extends over several vertebral levels. These tumors cause erosion of the posterior surfaces of the bodies of the vertebrae, thinning of the laminas and narrowing of the pedicles, with resultant increase in the interpedicular distances.

Erosion of the body is usually recognized later than changes in the laminas or pedicles. This may be due to the resistant action of the posterior longitudinal ligament.

Elsberg and Dyke [12] measured 100 normal spines and noted that the outline of the pedicles of the lower cervical and upper thoracic vertebrae were circular, those of the middle and lower thoracic vertebrae were oval or kidney shaped and those of the lumbar vertebrae were oval, kidney shaped or triangular. They recognized that there are normal cervical and lumbar enlargements in the canal. They also determined the normal range of the interpedicular distances in adult vertebrae.

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11. Stookey, B.: Intradural Spinal Lipomas, Arch. Neurol. & Psychiat. **18**:16 (July) 1927.

12. Elsberg, C. D., and Dyke, G. G.: The Diagnosis and Localization of Tumors of the Spinal Cord by Means of Measurements Made on the X-Ray Films of the Vertebrae and the Correlation of Clinical and X-Ray Findings, Bull. Neurol. Inst. New York **3**:359, 1933.

In figure 8 the interpedicular distances of the 1 adult patient in our series are compared graphically with the normal range as given by Elsberg and Dyke.[12] The normal range is greatly exceeded, and the fusiform enlargement of the canal is evident.

Because no normal range for the interpedicular distances in children has been determined, we measured the interpedicular distances of the lower thoracic and lumbar vertebrae in 100 children—50 between birth and 5 years of age and 50 between 5 and 10 years of age. The range of normal for children was less than that for adults, as one would anticipate.

The interpedicular distances for the children with mixed tumors were compared graphically with the normal range for their respective age group. Figures 9 and 10 illustrate the increase in the size of the spinal

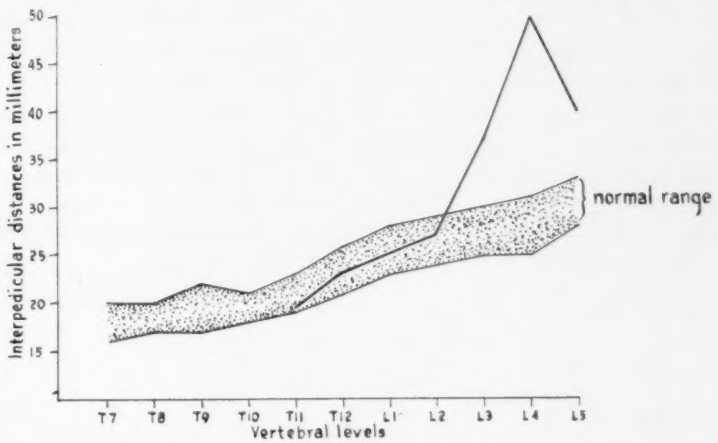

Fig. 8.—Measurements of the interpedicular distances in case 1 as compared with the normal range in adults.

canal in the children with mixed tumors. In case 3 (fig. 10) the normal range is not greatly exceeded, however, the increase of 4 mm. in the interpedicular distances of one level as compared with those of the adjacent levels was considered suggestive of abnormality. Elsberg stated that an increase of 2 to 4 mm. is significant.

It has been stated [12] that flattening of the pedicles is of significance only if the interpedicular distance is increased at the same level. In a series of 86 cases of tumor, Elsberg found flattening of the borders in 79 per cent of those in which interpedicular distance was increased, whereas in only 30 per cent of cases in which there was no increase were

13. Footnote deleted by the authors.

the borders flattened. Camp,[14] however, localized tumors on the basis of erosion of the laminas in all of a series of 23 cases, while he found the interpedicular distance at the level of the tumor to be within normal limits in 43.5 per cent. In these cases of mixed tumors, both flattening of the pedicles and increase in interpedicular distance was noted.

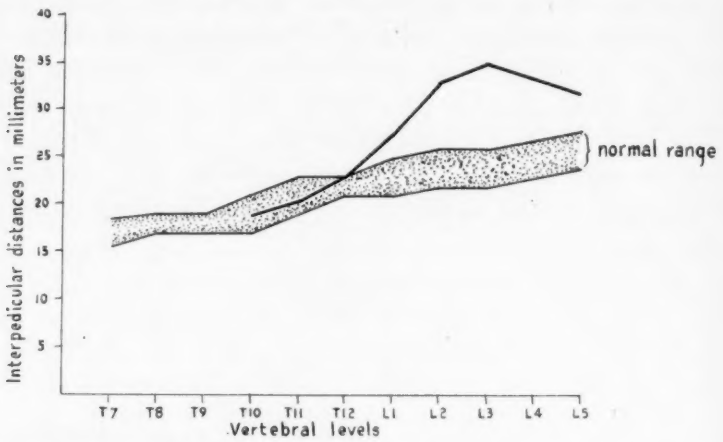

Fig. 9.—Measurements of the interpedicular distances in case 2 as compared with the normal range in children 5 to 10 years of age.

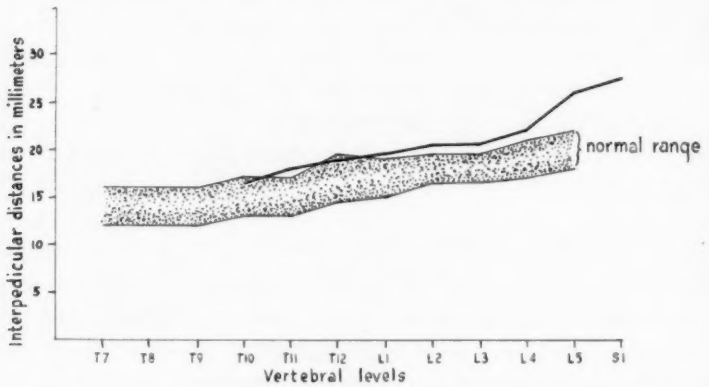

Fig. 10.—Measurements of the interpedicular distances in case 3 as compared with the normal range in children from birth to 5 years of age.

It was thought that it might be possible to determine abnormality in a vertebra without comparison with measurements of neighboring vertebrae by taking the ratio between the interpedicular distance and the

14. Camp, J. D.: Roentgenologic Contributions to the Localization of Tumors Affecting the Spinal Cord, Wisconsin M. J. **36**:621, 1937.

transverse diameter of the body of the vertebra, as seen in the antero-posterior roentgenogram ($\text{Ratio}=\frac{\text{Interpedicular distance}}{\text{Transverse diameter of body}}$). No consistent ratio was obtained for the same level in different patients or for different vertebral levels in the same patient; however, the ratio did vary consistently with the age of the patient. The ratio for children averaged 0.72, while that for adults averaged 0.60. This demonstrates that the body of the vertebra in children is relatively small in comparison with the spinal canal.

CONCLUSION

Three proved cases of mixed tumor of the spinal canal are presented.

Characteristic symptoms of mixed tumors are: (*a*) the long duration of symptoms before the patient becomes incapacitated; (*b*) the roentgenologic evidences of fusiform enlargement of the spinal canal with associated spina bifida.

The interpedicular distances of the lower thoracic and lumbar vertebrae in children were measured, and the normal range was found to be less than that of adults. In order to determine whether a spinal canal is enlarged, its measurements must be compared with the normal range in the subject's age group. A spinal canal that is larger than those within the normal range or the interpedicular distance of which increases 2 to 4 mm. in consecutive vertebrae shows evidence consistent with a diagnosis of mixed tumor.

THE BRAIN IN SICKLE CELL ANEMIA

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The central nervous system has not been examined with specific neuropathologic methods in any series of cases of sickle cell anemia. The present study is based on such a series of 5 unselected cases. Diagnostically questionable cases were ruled out. In all 5 cases lesions were present in the central nervous system.

The neuropathologic changes showed a great similarity in all cases, indicating a characteristic neuropathologic picture of sickle cell anemia.

REPORT OF CASES

CASE 1.—A Negress aged 28 had a history of migratory polyarthritis for five years. The patient was described as mentally peculiar, with a history of possible psychotic episodes and two suicidal attempts. She had once been to a medical clinic complaining of frequent "bleeding from below." Five days before admission an infection of the upper respiratory tract, with cough, chills and fever, developed. On the day of admission she was semistuporous and disoriented and complained of pain all over the body, especially in the arms, shoulders and legs.

Physical Findings.—Examination revealed scattered petechial hemorrhages in the skin, conjunctivas and eyegrounds; a questionable diastolic apical murmur; a greatly enlarged spleen, and marked anemia. The Wassermann reaction of the blood was 3 plus.

Course.—Left hemiparesis and convulsions developed, and the patient died after four days in the hospital.

Clinical Diagnosis.—The diagnosis was subacute bacterial endocarditis with cerebral embolism.

Gross Autopsy Observations.—There were marked hepatosplenomegaly, multiple petechial hemorrhages in the skin and conjunctivas, subpleural and subepicardial hemorrhages, pulmonary thrombosis with infarction, a normal heart and marked hyperplasia of the bone marrow. The brain showed no evidence of softening or hemorrhage.

Microscopic Observations.—Spleen: The pulp was greatly congested, and sickle cells were prominent here and in vessels. The sinusoids were compressed, only

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Read at the meeting of the American Association of Neuropathologists, Atlantic City, N. J., June 9, 1941.

remnants of follicles persisting. Occasional typical siderofibrotic nodules (Gandy-Gamna bodies) were present beneath the capsule and in the larger trabeculae.

Liver: The sinusoids were greatly congested with sickle cells.

Lungs: Antemortem thrombosis with hemorrhagic infarction was present.

Bone: The marrow showed hyperplasia, with prominent erythropoiesis. Sickling was noted within the capillaries. No focal necroses were seen.

Other Organs: A smear of heart blood taken post mortem showed many sickle cells. Considerable amounts of lipoid material were present in the glomerular loops and in pulmonary capillaries and small arterioles.

Final Anatomic Diagnosis.—The anatomic diagnosis was active sickle cell anemia; multiple cerebral capillary thrombosis; extensive focal encephalomalacia with hemorrhage; marked splenomegaly; splenic thrombosis with limited infarction; hepatomegaly; pulmonary thrombosis with infarction; subpleural hemorrhages; petechial hemorrhages of the skin and mucous membranes; hyperplasia of the bone marrow; extensive fat embolism of the brain, lungs and kidneys, and healed tubercles of the spleen and liver.

CASE 2.—A Negress aged 49 had a history of headache, dyspnea and nausea of two months' duration. Transient unconsciousness occurred seven years ago. Thirty-six hours before admission weakness became pronounced, the patient was unable to get about, headache became more severe and dyspnea was marked.

Physical Findings.—The blood pressure was 240 systolic and 140 diastolic, the heart was enlarged and the liver slightly enlarged. The Wassermann reactions of the spinal fluid and the blood were negative. The colloidal gold curve was 3332330000.

Course.—The patient lapsed into coma; rigidity of the neck developed, and she died five days after admission.

Clinical Diagnosis.—The diagnosis was hypertensive heart disease and cerebral hemorrhage.

Gross Autopsy Observations.—The spleen was approximately normal in size, with recent and old infarcts. The kidneys were very granular. A small yellowish tumor nodule was present in the submucosa of the ileum. There were marked hypertrophy and dilatation of the left ventricle. A specimen of heart blood taken one hour after death showed 40 per cent sickle cells. A large area of dark red hemorrhage occurred in the left basal ganglia, involving the internal capsule. A brownish, softened area was present in the region of the right basal ganglia. Another dark red hemorrhagic zone occurred in the anterior end of the right caudate nucleus. The lateral ventricles were dilated.

Microscopic Observations.—Spleen: There were marked engorgement of the pulp, compression of the sinusoids and marked dilatation and congestion of perifollicular capillaries, with prominent sickling throughout. A large recent infarct with an included arteriole showing a mural thrombus was observed.

Liver: There was prominent sickling, with engorgement of the sinusoids. One large vessel contained an agonal thrombus.

Lung: An isolated, recent infarct, with prominent sickling, was seen. No lipoid was present.

Kidney: Sickle cells were many, particularly in the region of vessels in the pyramids. Arterial and arteriolar sclerosis was noted. Occasional glomeruli contained lipoid material in considerable amounts.

Ileum: A submucosal carcinoid tumor was observed.

Final Anatomic Diagnosis.—The anatomic diagnosis was latent sickle cell anemia; old and recent cerebral hemorrhages in the right basal ganglia; recent

cerebral hemorrhage in the left basal ganglia; recent and old infarcts of the spleen; marked hypertrophy and dilatation of the left ventricle; myocardial fibrosis; coronary atherosclerosis; pronounced arteriolar nephrosclerosis; pyelitis cystica; fibrous pleuritis; old pelvic inflammatory disease; fibromyomas of the uterus; diverticula of the cecum and ascending colon; cholesterosis of the gallbladder, and carcinoid tumor of the ileum.

CASE 3.—A Negro aged 65 had a history of urinary incontinence for the past three months.

Physical Findings.—The bladder was distended to the umbilicus. The prostate was enlarged. The blood pressure was 250 systolic and 120 diastolic. The urine was frankly bloody. The Wassermann reaction of the blood was negative.

Course.—Uremia developed; the patient became confused and disoriented and died one month after admission.

Gross Autopsy Observations.—Autopsy revealed marked hypertrophy of the prostate; membranous cystitis, ureteritis and pyelitis; acute and chronic pyelonephritis; marked hypertrophy of the left ventricle, and old infarct of the spleen. A large softening was observed in the left parieto-occipital cortex and the subcortical white matter; a smaller softening was present in the right internal capsule and a small hemorrhage in the pons.

Microscopic Observations.—Spleen: A siderofibrotic nodule of the capsule and limited congestion of the pulp, with perifollicular engorgement, were observed. Some erythrophagocytosis and prominent sickling were present.

Kidney: Pyelonephritis, purulent casts in the tubules and numerous abscesses were noted.

Liver: The sinusoids were engorged, with prominent sickling.

Lung: Bronchopneumonia and pulmonary edema were present. No intravascular lipoid material was noted.

Final Anatomic Diagnosis.—The anatomic diagnosis was hypertrophy of the median bar of the prostate; prostatic calculi; membranous cystitis, ureteritis and pyelitis; acute and chronic pyelonephritis with multiple abscesses of the kidneys; nephrolithiasis; uremia; cerebral arteriosclerosis; softening of the left parieto-occipital region of the brain; softening of the right internal capsule; recent hemorrhage of the pons; coronary atherosclerosis; hypertrophy of the left ventricle; bronchopneumonia; pulmonary edema; latent sickle cell anemia, and old infarct of the spleen with limited siderofibrosis.

CASE 4.—A Negro aged 56 had a history of symptoms of gastric ulcer for many years, with a recent episode suggesting perforation. Operation soon after admission showed perforation. Gastrorrhaphy was done, but the patient died soon after.

Gross Autopsy Observations.—Autopsy revealed duodenal and gastric ulcers; paralytic ileus; perforations of the ileum with generalized peritonitis; bronchopneumonia, and fibrosis of the spleen. A small softening was present in the lower part of the pons.

Microscopic Observations.—The splenic pulp was congested, with some perifollicular dilatation of the sinusoids. Considerable sickling was present. Lobar pneumonia and extensive diffuse esophagitis were observed. No intravascular fat was seen in the liver, spleen, kidneys or pancreas. A few large capillaries in the heart contained lipoid material.

Final Anatomic Diagnosis.—The anatomic diagnosis was gastric ulcers; status postgastrorrhaphy; ileus of the small intestine; perforations of the ileum; gen-

eralized peritonitis; acute esophagitis; bronchopneumonia; arterial nephrosclerosis; fibrosis of the spleen; sicklemia, and focal pontile encephalomalacia.

CASE 5.—A Negro aged 31 had a history of recurrent episodes of jaundice and numerous ulcers of the leg for many years. Severe gas pains occurred intermittently. The patient was admitted in semicoma, with a history of sudden onset of headache and stiffness of the neck while at work.

Physical Findings.—The patient was semicomatose. The scleras were jaundiced. The heart was enlarged, with an apical diastolic murmur. Many healed ulcers occurred over the lower portions of both legs. Nuchal rigidity was present. There were paresis of the left side of the face and of the arms and paralysis of the left leg. The deep reflexes on the right were overactive; a Babinski sign was elicited on the right. The pupils were fixed to light and dilated. The temperature was 102 F. Urinalysis revealed a 4 plus reaction for albumin, a positive reaction for urobilinogen in a 1:320 dilution and the presence of bile. There were pronounced secondary anemia and moderate leukocytosis. A blood smear showed many sickle forms. Spinal tap revealed an initial pressure of 460 mm. of water. The fluid was xanthochromic and opalescent. The smear of the spinal fluid showed numerous sickle cells. A fragility test of the blood showed increased resistance.

Course.—The temperature rose to 104.6 F.; the patient had generalized convulsions and died three days later.

Clinical Diagnosis.—The diagnosis was sickle cell anemia with hemolytic crisis; subarachnoid hemorrhage; multiple softening of the brain, and rheumatic heart disease.

Gross Autopsy Observations.—Autopsy revealed a small congenital aneurysm of the left middle cerebral artery, with rupture and massive subarachnoid hemorrhage at the base of the brain; another small, unruptured aneurysm of the right middle cerebral artery located in symmetric relation to the first; pronounced fibrosis and contraction of the spleen; focal infarct of the liver; several small calculi of the gallbladder and common bile duct, with no obstruction, and marked hyperplasia of bone marrow.

Microscopic Observations.—Spleen: Confluent siderofibrotic nodulation was conspicuous throughout the spleen. The pulp was congested, with compression of the sinusoids. There was complete loss of follicular structure. Sickling was prominent within the pulp and intravascularly. The sinusoids were dilated.

Kidney: The glomerular tufts were greatly engorged, with sickle cells present throughout.

Liver: There was marked swelling of the liver cells, with small focal necroses. Large numbers of sickle cells were present throughout.

Bone: Erythropoietic hyperplasia was pronounced. Adult and some nucleated red cells showed distinct sickling. No focal necroses were seen.

Lymph Nodes: Blood pigment was present in sinusoidal endothelium. No intravascular lipoid material was observed in the liver, spleen or kidneys. Postmortem examination of the blood revealed 500 mg. of fatty acids per hundred cubic centimeters.

Final Anatomic Diagnosis.—The diagnosis was ruptured aneurysm of the left middle cerebral artery; subarachnoid hemorrhage at the base of the brain; active sickle cell anemia; multiple focal encephalomalacia; marked fibrosis and contraction of the spleen; focal infarcts of the liver; jaundice; marked hyperplasia of the bone marrow; hypertrophy of the left ventricle; congestion of the liver; old myocardial infarct, and chronic cholecystitis, cholelithiasis, choledocholithiasis.

NEUROPATHOLOGIC CHANGES

Sickle Cells in the Central Nervous System.—The presence of sickle cells in the brain was the most conspicuous neuropathologic feature.

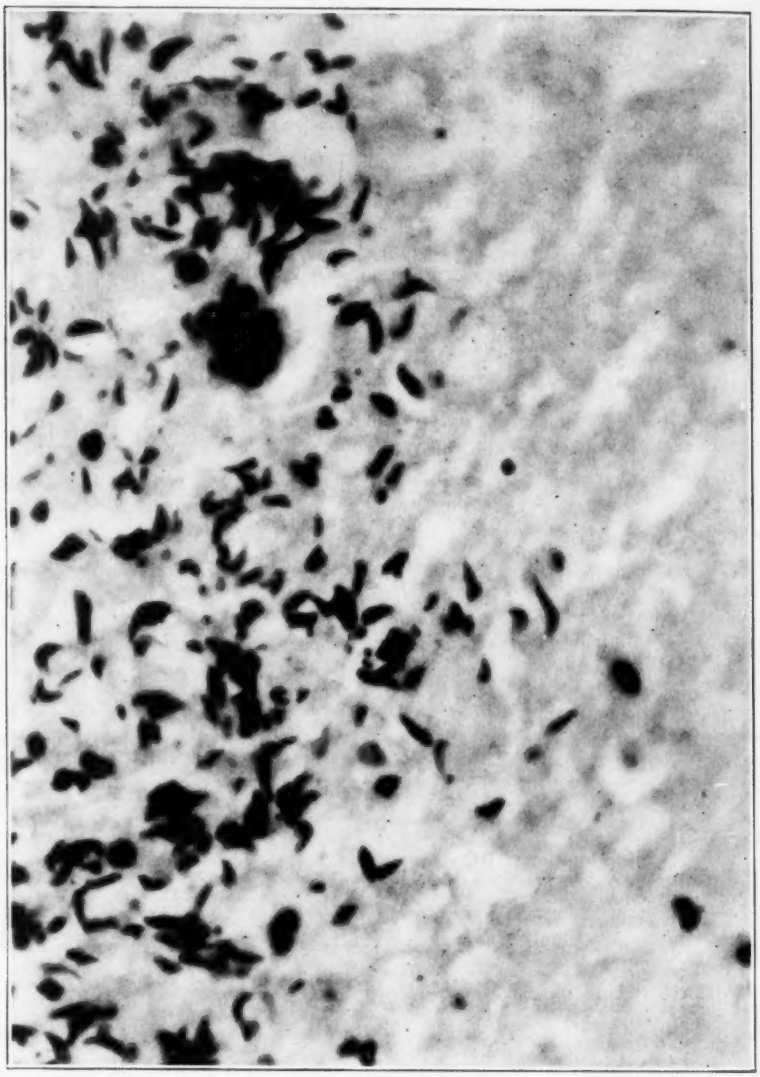

Fig. 1.—Sickle cells in brain tissue at the border of a hemorrhage. Anderson stain.

Such cells could be demonstrated best in the lumen of vessels in the arachnoid spaces. They had the typical appearance of such cells in the blood stream and in other organs of the body.

An interesting difference existed between the red blood cells in meningeal vessels at the tops of the convolutions and those in the depths of the sulci. Sickle cells were more likely to be seen deep in the sulci. It was sometimes striking how in the same region sickle cells were sparse or absent in vessels at the surface of a convolution but present in great numbers in the adjoining sulcus.

In case 5, in which there was a subarachnoid hemorrhage, sickle cells could be demonstrated in the spinal fluid in great numbers. In 1 case sickle cells suggestive of the granular forms described by Sherman [1] were seen, but this observation remained isolated and doubtful.

Large Vascular Lesions.—Large vascular lesions, recent or old, occurred in 3 cases. The sites of these vascular lesions were the basal ganglia, the parieto-occipital region and the pons.

Small Focal Lesions.—Far more characteristic were small focal lesions, which occurred in almost any region of the brain. These lesions were present in various forms and in various stages, apparently corresponding to the waves of activation, or crises, of the disease.

In the most severe and acute lesions there was complete circumscribed destruction of tissue, with development of a spongy state. Small softenings, with the formation of scavenger cells, also occurred, but were the exception. Some small lesions resembled in form the typical circulatory type.[2]

In Nissl preparations small, sharply delimited, pale areas could be demonstrated. They were observed most frequently in the cortex but reached also into the white matter, where they were more difficult to demonstrate.

Small areas of demyelination occurred in many areas of the brain, mostly in the white matter, but typical areas could also be seen in the cortex. Sometimes smaller round lesions became confluent. There were also areas of more diffuse thinning out of myelin fibers. In these lesions all the typical signs of degeneration of individual myelin fibers, such as swelling, distortion and formation of "strings of beads," could be demonstrated.

Some of the focal lesions were isolated; others were more or less regularly distributed over considerable areas. Some were in rows of two or three, indicating their development along the course of blood vessels. They occurred in the white matter, in the cortex and in the subcortical gray structures. Sites of predilection were the border region between the cortex and the subcortical white matter, including the

1. Sherman, I. J.: The Sickling Phenomenon, with Special Reference to the Differentiation of Sickle Cell Anemia from the Sickle Cell Trait, Bull. Johns Hopkins Hosp. **67**:309 (Nov.) 1940.

2. Wertham, Frederic, and Wertham, Florence: The Brain as an Organ, New York, The Macmillan Company, 1934, plate 77.

lowest parts of the cortex; the cerebellum; both the cortex and the white matter, especially the dentate nucleus and surrounding areas; the pons, and the cornu ammonis. In the last-named structure the

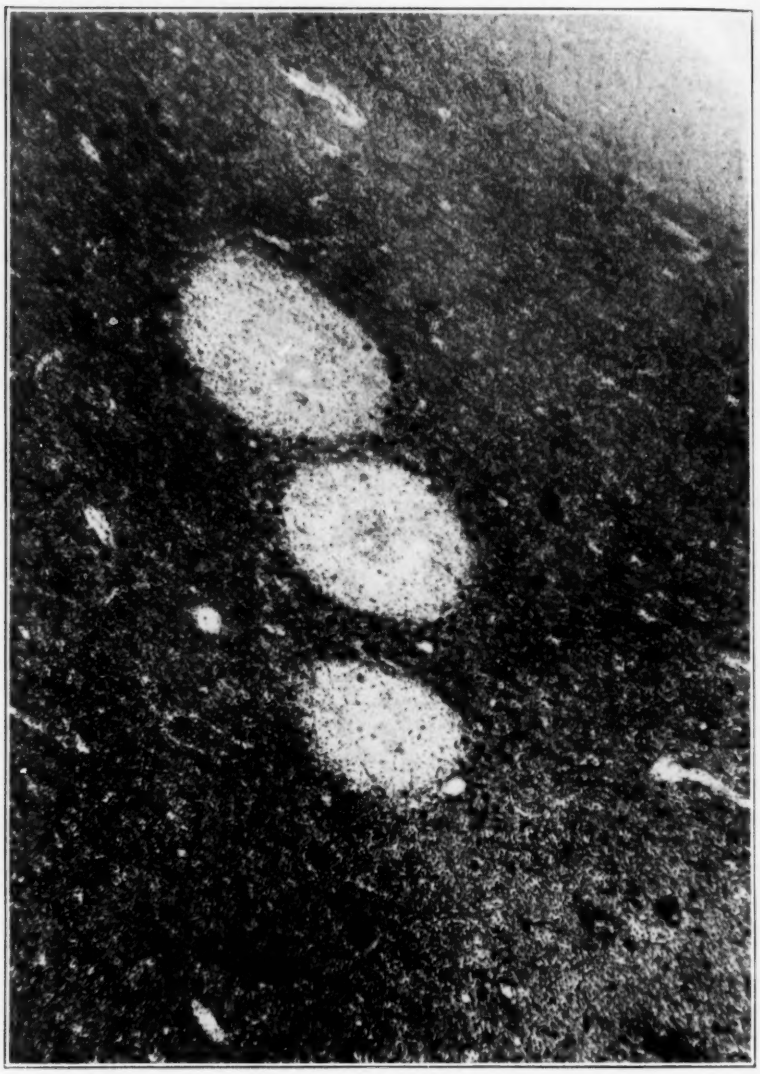

Fig. 2.—Three focal lesions in the subcortical white matter. Stain for myelin, counterstained with carmine.

Sommer sector did not appear to be especially affected and the lesions for the most part were of the same small, circumscribed type occurring elsewhere in the brain.

In the center of some lesions there were small hemorrhages or extravasations. In other areas there was blood in the tissue at the border of lesions and in the adjacent regions. Some of these focal lesions may have been due to small hemorrhages, but in the majority of the lesions hemorrhages were probably not the primary cause and the extravasations had taken place only secondarily, and in the preagonal phase of the disease. Emigration of leukocytes into the adventitial spaces and also into the surrounding tissue could be seen in vessels filled exclusively with sickle cells or with sickle and normal red cells and leukocytes.

Focal Glia Proliferations.—Focal proliferation of glia occurred but played a subordinate part. In some instances a central congested blood vessel could be demonstrated, while in others a small central necrosis could be seen. These foci had the same distribution as the small focal lesions without glial proliferation.

Alterations of Blood Vessels.—The outstanding change in the vascular system was pronounced hyperemia, especially in the small veins of the most peripheral portion of the vascular bed. It was most conspicuous in the cerebral cortex, in the cerebellum and near the ventricles. In some of the congested blood vessels sickle cells could be demonstrated. Thrombosis of small vessels occurred but did not seem to play an essential role in the pathogenesis of these lesions. Many were apparently agonal.

In many regions of the brain, in both the white and the gray matter, small blood vessels stood out conspicuously. This was due to two factors, which operated either alone or in conjunction with each other. The first was the congestion of these vessels. For example, many capillaries stood out in Nissl sections on account of their engorgement. The second was the fact that many small blood vessels, especially arterioles, were greatly thickened. In Nissl preparations blood vessels were conspicuously stained. There was practically no infiltration with round cells, but there were proliferation and increase in size of both the endothelial and the adventitial elements. These vessels resembled strongly the intracerebral vessels in meningitis.[3]

In glia fiber preparations, one gains the impression that there is proliferation of the fibrous glia adjacent to the larger vessels deep in the subcortical white matter. In view of the great variability of the glia fiber picture near vessels in different persons at different ages and in different regions of the brain, this observation cannot be definitely established as significant in conjunction with the pathologic process of sickle cell anemia.

3. Wertham, F.: The Cerebral Lesions in Purulent Meningitis [fig. 12], Arch. Neurol. & Psychiat. **26**:549 (Sept.) 1931.

Frequently, the small focal lesions previously discussed occurred near greatly congested vessels. In some areas small congested vessels were demonstrable in the center of the lesions. In other areas, one could follow a small congested precapillary vessel from the outside of a lesion through a glial wall to the center of the lesion.

Fig. 3.—Lesions in the subcortical white matter at the border of the cortex and extending into the cortex. Myelin sheath stain.

Necrosis of vessel walls did not appear to play a significant role. One could see small hemorrhages from precapillary vessels with a protoplasmic glia reaction around the hemorrhage, which in some instances appeared to be due to such a necrosis. The degeneration of cells of the vessel walls, however, might occur secondary to the hemorrhage.

Changes in Nerve Cells.—Morbid alterations of nerve cells, without predominance of any special type, occurred in various parts of the brain. They might be pronounced in the cortex, especially in the neighborhood of small focal lesions and congested vessels, but were also present at a distance from them. The Purkinje cells seemed to be particularly affected, showing changes of varying degrees up to complete disappearance, even in regions of the cerebellum where there were no focal lesions. The granular layer of the cerebellum, aside from some small focal lesions, exhibited in places diffuse diminution of the granular cells involving a whole lobule. The cells of the dentate nucleus also showed degenerative changes, especially when there were small lesions in the subcortical white matter of the cerebellum. Nerve cell changes in diffuse distribution occurred also in other subcortical gray structures, such as the basal ganglia, the hypothalamus and the corpus mamillare.

Siderotic Pigment.—An interesting observation in sickle cell anemia is the occurrence of siderotic pigment in the vessel walls. It occurred as small granules and in larger clumps. Sometimes it could be demonstrated near places where there were many sickle cells, but it was also present where sickle cells were not demonstrable. In the vessel walls, siderotic granules could be seen free in the intra-adventitial spaces of small and large vessels and within adventitial elements. Only in rare instances was such pigment seen in the tissue. This pigment is somewhat similar to that found in cases of dementia paralytica and of a spontaneous disease of chickens.[4] The essential difference is that, in contrast to these conditions, it does not occur in sickle cell anemia in such completely diffuse distribution and that it is not so predominant in the smaller vessels.

In sickle cell anemia this pigment is definitely hematogenic. Whether it is histochemically identical with "dementia paralytica iron" cannot be definitely stated, but in some cases its distribution in adventitial spaces and elements is so much like that in dementia paralytica and the spontaneous encephalitis of chickens that at least the suggestion can be made that the as yet unexplained iron in these conditions may also be of hematogenic origin. Further comparative histopathologic and histochemical studies may clear up this point.

Intravascular Lipoid Material.—An important feature of sickle cell anemia, namely, the occurrence of lipoid material within capillaries and precapillary vessels of the brain, was recently pointed out by Wade and Stevenson [5] in a study of a case of sickle cell anemia. We can confirm

4. Wertham, F.: The Nonspecificity of the Histologic Lesions of Dementia Paralytica, Arch. Neurol. & Psychiat. **28**:1117 (Nov.) 1932.

5. Wade, L. J., and Stevenson, L. B.: Necrosis of the Bone Marrow with Fat Embolism in Sickle Cell Anemia, Am. J. Path. **17**:47 (Jan.) 1941.

their observations in 2 of our cases (1 and 5). In case 1 fat was also present in considerable quantity in the kidneys and lungs. In case 5 no fat was found in other organs of the body. In case 1 fat was present

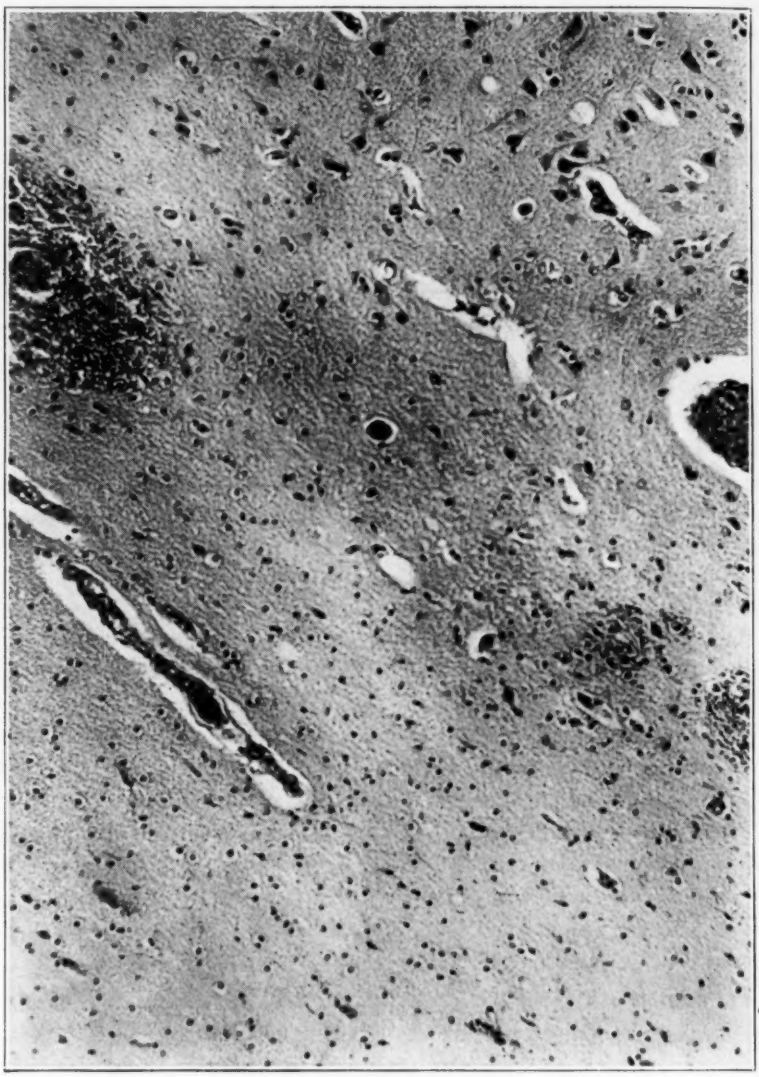

Fig. 4.—Focal perivascular gliosis. Nissl stain.

in the small vessels of the brain. In some instances capillaries filled with fat could be demonstrated within small focal lesions or at the border of lesions. In others fat-filled vessels could be demonstrated where lesions were absent. In case 5 lipoid material occurred in the brain, but in much smaller quantity.

Evidently, many of the small focal necroses are due to fat embolism. But the relative distribution of focal lesions, of fat, of congestion and thrombosis and of the other morbid alterations of the tissue gives us

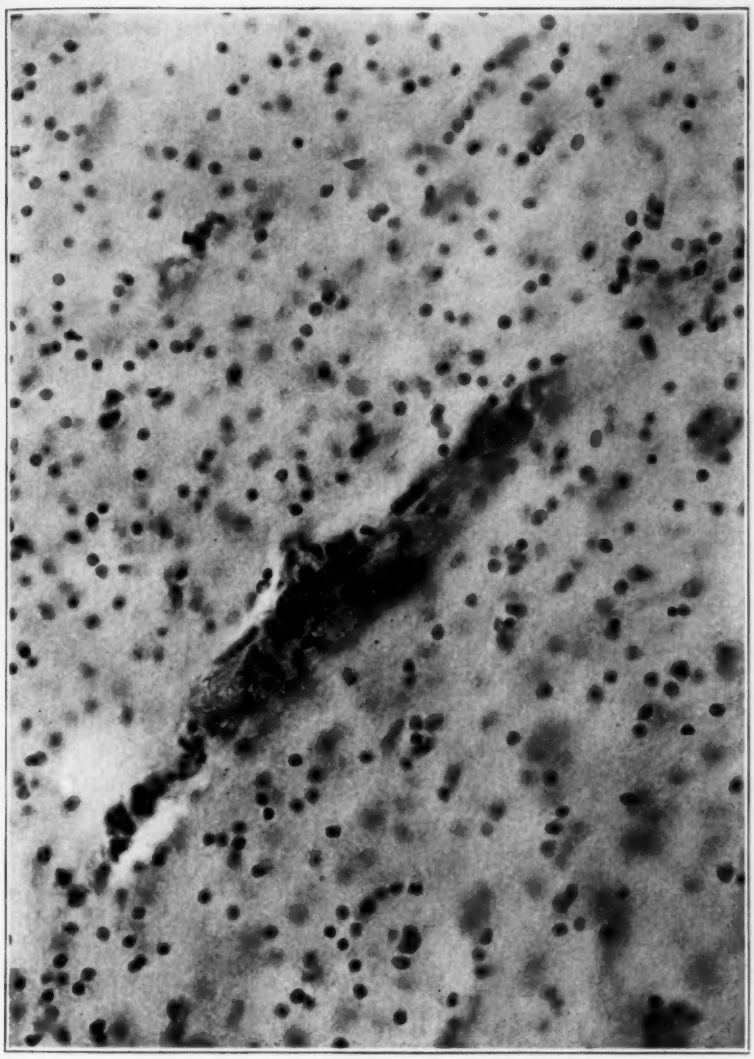

Fig. 5.—Siderotic pigment in intra-adventitial spaces and in adventitial cells of a small vessel. Turnbull blue stain.

the impression that fat embolism is not the only, or the predominant, factor in the pathogenesis of the neuropathologic changes described.

In nile blue sulfate stains the material that gave a positive reaction with the sudan III stain took on a violet color, suggesting that it was

not neutral fat but some form of lipoid. This was true of the material not only in the vessels of the brain but in the other organs.

The presence of fat embolism, as pointed out by Wade and Stevenson, is undoubtedly significant. Vance,[6] in a study of 82 cases in which the origin was nontraumatic, found only "very slight fat embolism" in 7. The presence of fat in the capillaries in cases of sickle cell anemia has

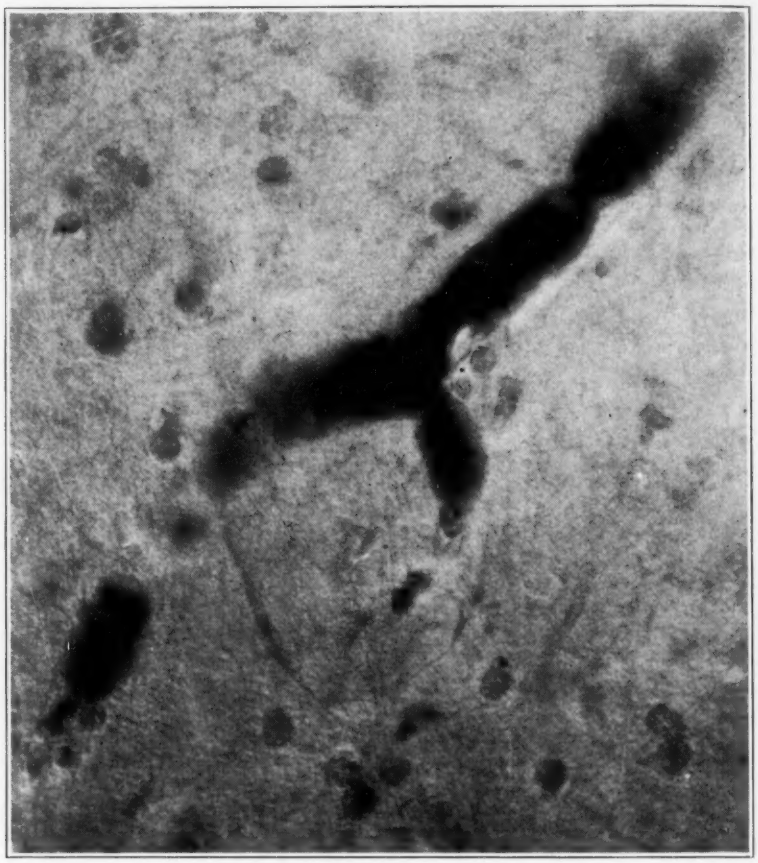

Fig. 6.—Lipoid material in a precapillary in the brain. Herxheimer stain for fat.

been described by Wollstein and Kreidel,[7] who observed fat in the heart, and by Brittingham and Phinizy.[8] The latter authors observed a large amount of fat in the brain, lungs, heart, liver, spleen, adrenal glands,

6. Vance, cited by Wade and Stevenson.[5]

7. Wollstein, M., and Kreidel, K. V.: Sickle Cell Anemia, Am. J. Dis. Child. **36**:998 (Nov.) 1928.

8. Brittingham, J. W., and Phinizy, T.: Hemorrhagic Encephalitis After Neoarsphenamine, J. A. M. A. **96**:2021 (June 13) 1931.

kidneys and pancreas in a case of hemorrhagic encephalitis with coexistent sicklemia resulting from arsenical poisoning. It is noteworthy that in only 1 of our cases was the "fat embolism" extensive. We doubt that the origin of this fat is in the bone marrow, as suggested by Wade and Stevenson. In none of our cases was necrosis or emulsification of fat

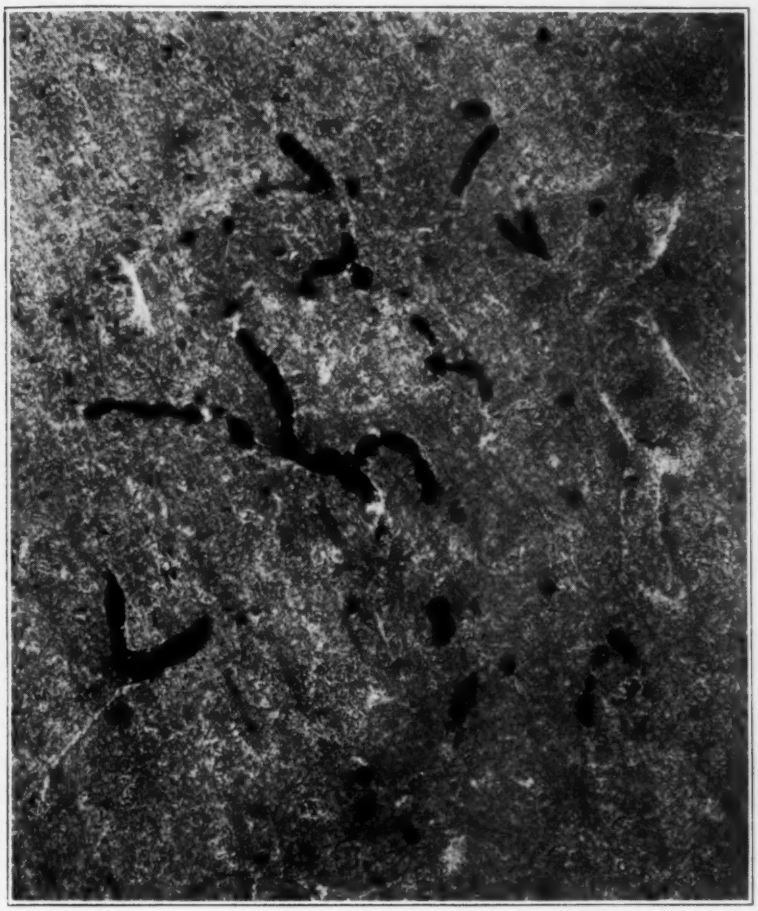

Fig. 7.—Fat embolism in the brain. Nile blue sulfate.

observed in the bone marrow. Coupled with this fact is the observation that intravascular material which gave a positive reaction with sudan III stained like lipoid, and not like neutral fat, with nile blue sulfate. It is possible that some obscure alteration in lipoid metabolism is involved in the phenomenon of sickling, in the occurrence of thrombosis, in the phenomenon of hemolysis and in the appearance of intravascular lipoid in considerable quantity.

In cases 2, 3 and 4 no intravascular lipoid material was observed in the brain or other organs.

Spinal Cord.—The spinal cord was fully examined in only 1 of our cases. Histopathologic study of this cord bore out the prediction made by Hughes, Diggs and Gillespie:[9] "Future studies will reveal gross spinal cord lesions in some cases." The lesions in the spinal cord can be most succinctly described as being like those in subacute combined degeneration. In many segments of the cord, especially in the cervical and lumbar regions, small areas of demyelination are present, mostly in the posterior and less in the lateral columns. Some were near greatly distended blood vessels. In some segments, Nissl stains showed marked gliosis of one anterior horn with degeneration of nerve cells and much less pronounced gliosis in both posterior horns.

COMMENT

The diagnosis of sickle cell anemia, when neuropsychiatric manifestations predominate, is apparently often missed. In 4 of our 5 cases the diagnosis was made only post mortem, by examination of the organs and blood. Symptoms referable to the central nervous system seem often to have been diagnostically misleading, for in many clinical reports of sickle cell anemia they have been regarded as merely incidental. Neuropsychiatric symptoms of wide variety and diverse localization occur frequently in cases of sickle cell anemia. In 1 of our cases there was a history of past psychotic episodes. In diagnostically difficult cases of exogenic psychosis, with or without focal symptoms, especially in Negroes, the possibility of a crisis in sickle cell anemia must be considered. It seems likely that in cases of severe, active sickle cell anemia the central nervous system is usually involved in the pathologic process.

The mechanism of causation and evolution of the neuropathologic alterations in sickle cell anemia is not clear, just as no known cause exists for the phenomenon of sickling itself. Some significance must be given to the occurrence of hypertensive vascular disease in cases 2 and 3 in association with the larger vascular lesions observed.

The role of the hemolytic crisis in sickle cell anemia in the causation of the neuropathologic changes is unknown. In case 1 no evidence of hemolysis was present, although severe secondary anemia was noted. In case 5 a marked hemolytic crisis was apparent, with less extensive involvement by small focal lesions.

Despite the occurrence of complications in unselected cases of sickle cell anemia in which an autopsy has been performed and despite the great variations in number, distribution and stages of the morbid changes in the brain, it seems possible to clarify the neuropathologic picture.

9. Hughes, J. G.; Diggs, L. W., and Gillespie, C. E.: The Involvement of the Nervous System in Sickle Cell Anemia, J. Pediat. **17**:166 (Aug.) 1940.

SUMMARY

The essential neuropathologic features of sickle cell anemia are small, necrotic and necrobiotic lesions on a vascular basis, diffusely distributed, with predilection for the border between the cortex and the subcortical white matter; marked general hyperemia and congestion of blood vessels; hypertrophy and proliferation of endothelial and adventitial elements of the walls of small blood vessels; siderotic pigment in intra-adventitial spaces and adventitial cells; larger vascular lesions of uncharacteristic type (softenings, thromboses, etc.); small hemorrhages and extravasations; intravascular lipoid material and fat embolism of capillaries and precapillaries; focal and diffuse changes in the nerve cells in cortical and subcortical gray structures, and focal areas of demyelination in the spinal cord, similar to those seen in subacute combined degeneration.

DISCUSSION

DR. ALFRED ANGRIST, New York: The demonstration of fat in the smaller blood vessels in the brain by Drs. Wade and Stevenson is of the utmost significance for the understanding of the clinical picture and, it is hoped, the pathogenesis of this disease entity.

It is open to question whether it has actually been established that the fat in the blood vessels originates from necrotic areas in the bone marrow and actually represents fat embolism in this sense. The abundance of the fat, the wide distribution of the lesions, the relative suddenness of onset—all would require widespread necrosis of fatty marrow with simultaneous emulsification and parallel absorption into the sinusoids of the marrow. Finally, one would expect the fat in the blood vessels of the brain to be neutral fat if it had this source, inasmuch as fatty marrow consists mainly of neutral fat. Histochemical studies, however, demonstrate that with nile blue sulfate this fat stains like lipoid, and not like neutral fat. Finally, no foci of actual necrosis of bone marrow were seen in routine sections in any of our own cases.

A suggestive unifying concept is intimated. It is well known that the shape of cells, and this includes erythrocytes, depends on a surface tension phenomenon, in good measure. It is further known that the cell membrane of the erythrocyte contains a considerable portion of the complex lipoids of the cell protoplasm. The basic anomaly which determines the shape of the cell may be linked with some biochemical lipoid disturbance. It is of interest, then, to note that the material found in the blood vessels of the brain and elsewhere in the body does stain like lipoid and that the phenomenon of crisis, which is known to occur in this disease, may result in the sudden liberation of such material until it appears free in the blood stream. Confirmation of this assumption would require careful biochemical study of the lipoids.

DIVERTICULA OF THE LATERAL VENTRICLES EXTENDING INTO THE CEREBELLAR FOSSA

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AND
F. L. McNAUGHTON, M.D.
MONTREAL, CANADA

Migration of the lateral ventricles from their normal position is a common occurrence and may be extreme. An expanding lesion almost invariably displaces the ventricular system away from it, while in many cases an atrophic lesion draws the ventricular system toward it. When the ventricles are enormously dilated, as in internal hydrocephalus, the brain and adjacent portions of the lateral ventricles may migrate through a defect in the skull. Protrusions from the lateral ventricle into the cerebellar fossa through the incisura tentorii are undoubtedly of rare occurrence. We are therefore reporting in detail a case of this kind, with the clinical and postmortem observations. The probable manner of formation of these "protrusions" and their ventriculographic interpretation will also be discussed.

REPORT OF A CASE

S. G., a girl aged 7½ years, was admitted to the Montreal Neurological Institute on Oct. 24, 1939. There was a history of whooping cough at the age of 3½ years, followed by persistent vomiting and malnutrition. The head was said to have increased considerably in size during the year following the whooping cough, that is, until three years before admission. Secondary sex characteristics had begun to develop one year before admission, though menstruation had not begun. Suboccipital pain and generalized headache had been present for two months, and two attacks of opisthotonos had occurred in the three weeks previous to her entrance to the hospital.

Examination.—Examination revealed marked enlargement of the head, the diameter being 56 cm. The child was completely blind in the left eye, with loss of the light reflex, and there was marked diminution of visual acuity in the right eye, with a probable temporal field defect. There were also weakness of the lower right side of the face, unsteadiness of gait with wide base, lack of coordination of the right leg and marked bilateral optic nerve atrophy. The musculature was poorly developed. Both breasts were markedly increased in size, and pubic hair was present.

Laboratory Data.—Urinalysis revealed nothing abnormal. Examination of the blood showed 6,200,000 red cells, 11,000 white cells and 85 per cent hemoglobin concentration. The Wassermann reaction of the blood was negative. The cerebro-

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spinal fluid pressure (taken at the time of ventriculographic examination) was over 700 mm. of water. The Wassermann reaction of the cerebrospinal fluid was negative; the proteins measured 33 mg. per hundred cubic centimeters, the Pandy reaction was negative and the fluid (ventricular) was clear and colorless. Assays of the urine for gonadotropin and estrogen were negative.

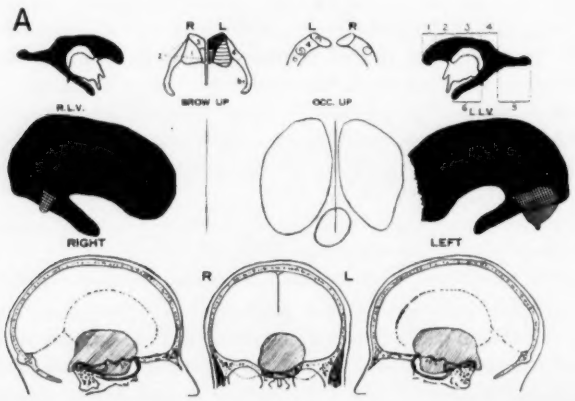
Roentgenographic Findings.—Plain roentgenograms of the skull showed the cranium to be decidedly larger than normal for a child of her age. Convolutional markings were moderately increased, and there was some very slight separation of the sutures. The outline of the sella was almost completely obliterated, and it was scarcely possible to recognize even the anterior clinoid processes. The basisphenoid and the basiocciput bulged downward, presenting a convexity of their inferior surfaces and resulting in obliteration of the sphenoid sinuses. The remaining sinuses were developing normally. There was no intracranial calcification. It was felt that the appearance indicated a long-continued increase in intracranial pressure which was progressing rather slowly, so that growth of the cranium had kept pace with the enlargement of the brain.

Roentgenographic examination of the knee, wrist and ankle showed ossification to be approximately two years further advanced than usual for a child of this age, although the long bones were thin and decalcified, probably because of disuse.

Ventriculographic examination was performed on November 4, 200 cc. of oxygen being injected directly into the lateral ventricles. These structures were so tremendously dilated that visualization was incomplete. A collection of oxygen was present in the midline in the posterior fossa, and it was thought that this possibly represented the posterior part of the fourth ventricle. The subarachnoid space was not visualized. Adhesive arachnoiditis, possibly in the neighborhood of the cisterna magna or the fourth ventricle, was suspected. The next day the child was reexamined after the introduction of an additional 400 cc. of oxygen into the ventricular system. The lateral ventricles were again seen to be enormously dilated. In roentgenograms made with the patient in the brow down position there were two shadows just below the apex of the tentorium. The larger had a diameter of almost 4 cm. Superiorly it seemed to communicate with the left lateral ventricle, but it was thought that this might well represent superimposition. At its lower pole there was a pointed projection, with a diameter of about 5 mm., which ran toward the foramen magnum for a distance of 8 or 9 mm. The smaller shadow lay just to the right of the first one. Superiorly its width was 1.5 cm., and it extended downward for 1.8 cm. Posteroanterior roentgenograms showed the larger shadow to lie in the midline and to extend slightly farther to the left than to the right. The smaller shadow was not visible in this direction. There was no definite visualization of the third ventricle in spite of adequate posturing. Altogether the appearance was confusing. A protrusion of the lateral ventricles into the posterior fossa should have been considered, but instead it was felt that the shadows probably represented a peculiarly displaced fourth ventricle. The final diagnosis was a large tumor situated adjacent to the base of the skull and rising upward and obliterating the third ventricle, as well as displacing the fourth ventricle backward and upward. These ventriculographic findings are summarized in figure 1.

Course.—Suboccipital craniotomy was performed later in the day by Dr. Wilder Penfield. At operation, the cerebellum appeared normal except that it was under greatly increased pressure. There was a collection of cerebrospinal fluid beneath the tentorium, above and anterior to the cerebellum; this was reached by puncture at a depth of 3 cm. from the horizontal sinus. On puncture fluid came out under

pressure, as well as oxygen which had been injected into the ventricles during the preceding ventriculographic examination. The cyst was later proved to be one of the protruded portions of the lateral ventricles, which will be described later. The fourth ventricle was collapsed and did not communicate with this space; its lower tip was within 1 cm. or less of the cisterna magna. In the left cerebellopontile angle the vagus and the seventh and eighth nerves lay over a cystic collection, which was anterior to them and pushed them backward. This cyst lay beneath the brain stem and obviously extended into the middle fossa. It was filled



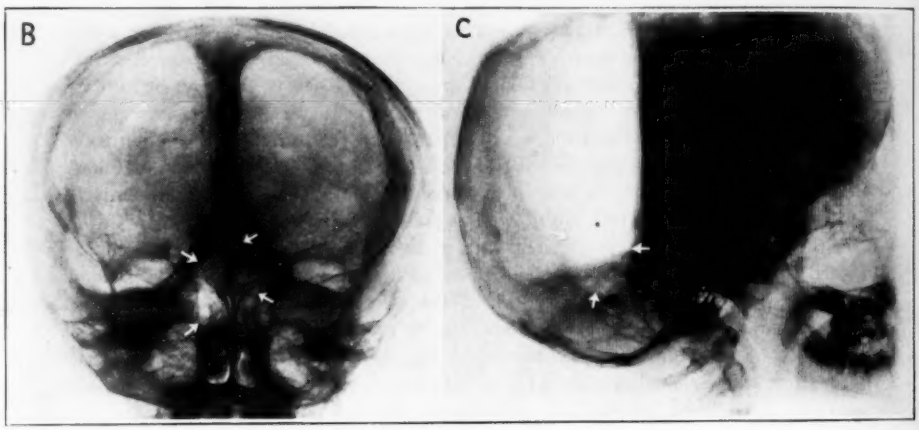


Fig. 1.—*A*, pneumographic analysis of the case, and *B* and *C*, pneumograms. *B* is a posteroanterior view and *C* a lateral view with the brow down, showing the outline of the large protrusion from the left ventricle. For details of the chart (*A*) see article by Childe and Penfield.[1]

with amber fluid, which was aspirated, and some of the cyst wall was cut away. More of the wall was then drawn out and the cavity irrigated. Some cerebellar tissue was subsequently sucked out to make a passage for the cerebrospinal fluid

1. Childe, A. E., and Penfield, W.: Anatomic and Pneumographic Studies of the Temporal Horn, Arch. Neurol. & Psychiat. **37**:1021-1034 (May) 1937.

from the subtentorial collection. At the end of the procedure Dr. Penfield stated that he could not be sure whether he was dealing with a cystic tumor which lay beneath the brain or with a hemorrhagic cyst, which might have been produced by the patient's coughing at the time of her attack of whooping cough, four years previously.

The following morning a second operation was performed by Dr. Penfield through a left temporal craniotomy. When the temporal lobe was retracted upward, a reddish, encapsulated tumor was exposed, rising through the incisura tentorii and passing forward in the midline. The left side of the tentorium was clipped and cut; with this exposure the tumor was incised, and as far as possible the neoplastic tissue was removed. It was hoped that this procedure might relieve the block in the cerebrospinal fluid circulation at the incisura tentorii.

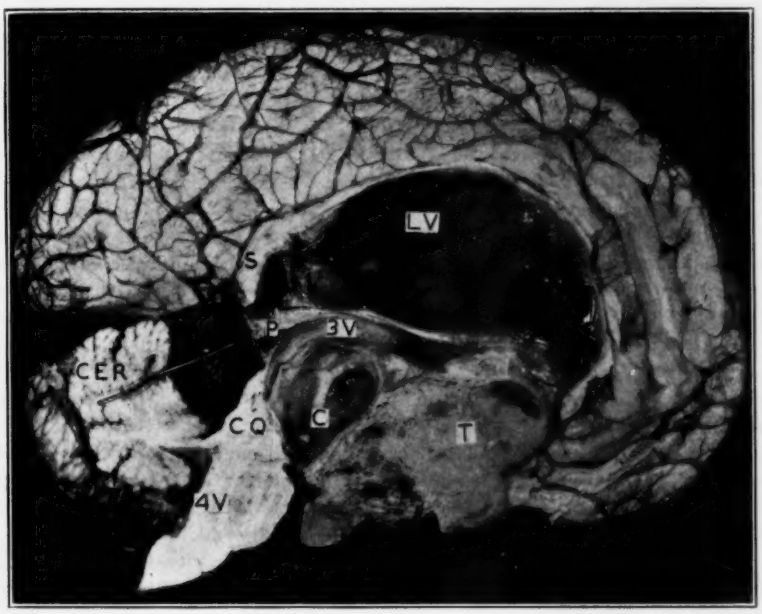


Fig. 2.—Photograph showing the medial surface of the left half of the brain, after median sagittal section. A probe passes from the greatly dilated lateral ventricle (*L V*) through the orifice below the splenium (*S*) into the left, cystlike cavity, which lies above and behind the corpora quadrigemina (*C Q*) and above and anterior to the cerebellum (*CER*). The downward displacement of the fourth ventricle (*4 V*) and the tubelike cavity of the third ventricle (*3 V*), which has been pushed upward by the growth of the tumor (*T*), with its large cyst (*C*), can be plainly seen. Another cyst can be seen hanging down in front of the pons. This was partly removed at operation. The interventricular foramen, with a tuft of choroid plexus in its roof, can be defined at the anterior end of the third ventricle. The aqueduct of Sylvius does not show on this half of the brain but was found to be patent up to its opening into the third ventricle. *P* indicates the pineal gland.

After the second procedure there was no relief of the cerebrospinal fluid block, and repeated ventricular punctures were necessary to control the high intracranial

pressure. The child reached a state of consciousness in which she would respond to verbal orders from her father, but later drifted into a deep coma and died on the sixth postoperative day.

Postmortem Observations.—The autopsy showed precocious development of the ovaries, mammary glands and external genitals and adult female distribution of hair. The uterus, however, was small. Examination of the brain showed a huge cystic polar spongioblastoma, which arose from the hypothalamic region and almost completely obliterated the third ventricle from below and pushed the midbrain backward (fig. 2). The hypothalamic structures, including the corpora mamillaria, appeared to be obliterated by the growth of the neoplasm. Each interventricular foramen was patent, and the lateral ventricles were very large and uniformly dilated. The septum pellucidum extended back to the under surface of the splenium and was greatly thinned; it showed an extensive defect. The corpus callosum was also very thin, except at the splenium. The cavity of the third ventricle was distorted by pressure from below, giving it a somewhat tubular shape, and at its posterior end the opening of the aqueduct of Sylvius was obstructed by the pressure of a large cyst lying below and in front of it. The aqueduct itself and the fourth ventricle were not dilated.

The pituitary gland was flattened on the floor of the sella turcica but histologically appeared normal. The pineal gland contained a hemorrhagic area, but the cellular structure otherwise appeared normal.

A protrusion from the left lateral ventricle had apparently taken place through the medial part of the floor of portion 4 and had extended into the cerebellar fossa, close to the apex of the tentorium. This had compressed and displaced the superior portion of the cerebellum downward and backward and distorted the upper portion of the roof of the fourth ventricle. An exactly similar, but considerably smaller, protrusion had occurred from the corresponding region of the right lateral ventricle.

Examination of the ventricular cavities from above (fig. 3) showed that these protrusions had taken place through the floor of the lateral ventricles, just in front of and beneath the splenium of the corpus callosum. The orifice on the left measured 1.2 by 1.2 cm. and led into a smooth-lined cavity continuous with the ependymal lining of the ventricle. This cavity measured 3 cm. in length, 3 cm. in height and 3 cm. in width; it extended across the midline. The orifice on the right was larger, measuring 1.5 by 2 cm., but the cavity itself was smaller than that on the left and measured approximately 2 cm. in length, 2 cm. in height and 1.5 cm. in width.

Each orifice was bounded above and behind by the fibers of the splenium (which curve posteriorly as the forceps major into the occipital lobes), together with the upper end of the hippocampus, which is attached to the inferior surface of the splenium at this point. The anterior boundary of each orifice was formed by the crus of the fornix on the same side and the posterior end of the thalamus. At this point the crus is curving laterally to reach the hippocampus, where it becomes the fimbria. Between the orifices lay the thinned-out posterior portion of the septum pellucidum.

It was evident that these abnormal openings had developed either by splitting the thinned-out crura of the fornix close to their attachment to the splenium or by separating the crura completely from the splenium. The latter seemed more likely.

The sacs lay side by side in the incisura tentorii and below it, in a space bounded in front and below by the quadrigeminal plate of the midbrain, behind and below

by the displaced cerebellum and superior medullary velum and above and to either side by the under surface of adjacent parts of the temporal and occipital lobes and the tentorial margins (fig. 2). The arachnoid membrane surrounding the two sacs could be easily separated from them and was reflected from the superior surface of the cerebellum onto the under surface of the cerebral hemispheres. These protrusions therefore lay within the subarachnoid space, in the upper portion of what would normally be the cisterna ambiens. The sacs did not intercommunicate, and there was no opening from them into the subarachnoid or the subdural space other than the one made at operation. The large veins which normally lie in this portion of the cisterna ambiens had been displaced upward or to either side, while the pineal gland was pushed forward.

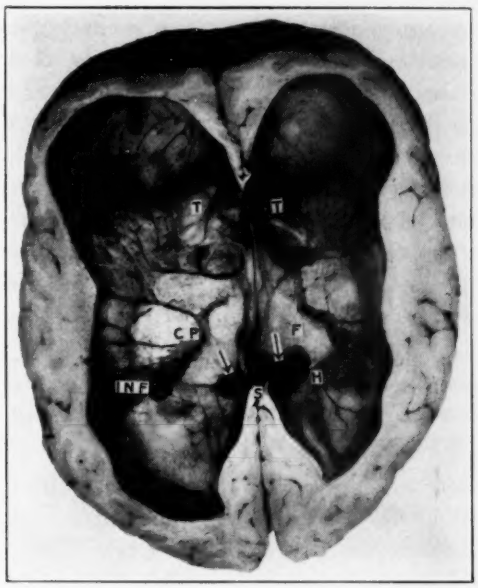


Fig. 3.—Photograph of the lateral ventricles, viewed from above, showing the two openings from the ventricles into the cavities, and the structures which surround them. The broad, thin crus of the fornix (*F*) lies in front of each opening, and laterally it joins the hippocampus (*H*) to become the fimbria. The choroid plexus of the lateral ventricle (*C P*) is attached to the free lateral border of the body and crus of the fornix on each side and can be seen disappearing into the inferior horn (*INF*) with the hippocampus and fimbria. Behind the openings lie the fibers of the splenium (*S*). At *T* and *T* the tumor is seen bulging into the floor of the ventricle and flattening the pillars of the fornix.

On microscopic examination the walls of the sacs were composed of loosely arranged collagenous bundles, containing fibroblasts. The lining consisted of a poorly defined layer of cells with slightly oval nuclei, which did not resemble the ependymal cells lining the walls of the lateral ventricles and were more likely of mesodermal origin.

COMMENT

Though this case presents a number of interesting features, including pubertas praecox, discussion will be limited to the peculiar cavities, their mode of production and the ventriculographic interpretation.

The autopsy observations cleared up the previously confusing diagnosis made from the ventriculograms. It became obvious that the shadows originally considered to be the fourth ventricle represented the protrusions from the lateral ventricles into the cerebellar fossa. In none of the films was there any visualization of the fourth ventricle, nor was the third ventricle shown. Fortunately, the erroneous interpretation correctly localized the tumor.

The first note of such a protrusion which we have found in the literature is that of a case described by Penfield.[2] In his case there was marked internal hydrocephalus, due to a cholesteatoma of the third ventricle blocking the foramen of Monro. The most interesting clinical feature was the occurrence of attacks of "diencephalic autonomic epilepsy." The lateral ventriculogram, taken with the brow down, showed a shadow distinct from, and partly below, the shadow of the dilated posterior horns. This was thought at the time to lie above the tentorium and between the occipital lobes. At postmortem examination it was stated:

> The posterior end of the corpus callosum was raised, and a defect through it caused a communication to exist between the lateral ventricle of each side and a cystic cavity bounded above by the cerebral hemispheres, posteriorly by the cerebellum and below by the roof of the midbrain.

It is clear that there was one cavity, and not two, as in the case we have described, but this was undoubtedly a protrusion from the lateral ventricles into the posterior fossa of the same type.

Peterson,[3] of Minneapolis, recently described a similar condition. He has permitted us to cite his case, in which there was a protrusion from the left lateral ventricle only into the cerebellar fossa. The man, aged 30, had a history of spells of unconsciousness for five months before admission. A ventriculogram showed good filling of the lateral ventricles and third ventricle and filling also of a cystic area in the midline in the usual location of the aqueduct. It was thought that this area might represent a cystic tumor which was communicating with the ventricles and causing partial obstruction of the aqueduct. The patient died eight days after craniotomy. Postmortem examination showed tremendous dilatation of the lateral ventricles, the third ventricle and the rostral portion of the aqueduct. The aqueduct was completely occluded in its

2. Penfield, W. G.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358-374 (Aug.) 1929.

3. Peterson, H. O.: Personal communication to the authors.

midportion. The posterior horn of the left lateral ventricle showed a herniated cyst, which had extended posteriorly and was situated along the superior border of the cerebellum. The cyst connected only with the left lateral ventricle and appeared to be an extension of this structure. Microscopic examination showed a diffuse astrocytoma involving the mesencephalon.

A third case was reported in detail by Sweet [4] while this paper was in preparation. His case was that of a boy of 14 with a history of mental retardation for six years and later development of obesity, unsteadiness of gait, dimness of vision and, finally, attacks in which the head was thrown back and the eyes rolled up. Ventriculographic examination was not made, and there was no operation. Autopsy revealed an infiltrating astrocytoma of the pons and midbrain, occluding the rostral portion of the aqueduct and producing enormous dilatation of the third and lateral ventricles. An abnormal opening from the right lateral ventricle between the splenium and the right crus of the fornix opened into a well defined cavity in the posterior fossa, occupying the same position as the larger cavity described in our case and measuring 2 by 2 by 3.5 cm. It did not communicate with the subarachnoid space, and the arachnoid membrane overlying it could be separated from it. From Sweet's description there is no doubt that the cavity was of the same abnormal type as that described in our case, though in his case, as well as in Peterson's, the saclike protrusion developed on one side only.

In examining a series of brains from the Montreal Neurological Institute showing marked internal hydrocephalus, due to various causes, we have found no other example of such an abnormal cavity or cavities. However, in several brains we noted thinning out and hollowing of the crura of the fornix close to their attachment to the under surface of the corpus callosum, as though a protrusion was beginning to develop at this point. If sought for, such a condition would probably prove to be more common than has been suspected before.

How are these abnormal cavities formed? As Sweet suggested, it seems likely that rupture occurs through a weak point in the ventricular wall, with formation of a new cavity beneath the pia mater communicating with the ventricle. Gross and microscopic study of our specimen tends to confirm this view.

Examination of the coronal section of a hydrocephalic brain shown in figure 4 indicates how thin and relatively weak the crura of the fornix may become in some cases. The crura are stretched like a roof above the corpora quadrigemina, in the incisural opening, and are quite unsupported from below. It is clear that this is the weakest point in the wall

4. Sweet, W. H.: Spontaneous Cerebral Ventriculostium, Arch. Neurol. & Psychiat. **44**:532-540 (Sept.) 1940.

enclosing the lateral ventricles. When there is internal hydrocephalus with high supratentorial pressure, it is easy to see how the crura might be split or separated from the splenium and allow formation of a new cavity or cavities, surrounded by pia, lying in the cisterna ambiens and communicating with the lateral ventricles.

It would appear that two main conditions are necessary for the development of protrusion of one or both lateral ventricles in this situation. First, there must be increased pressure within, and presumably marked dilatation of, the lateral ventricles. The second essential feature is the lack of any large space-occupying lesion in the cerebellar fossa which might tend to make pressure in this region as high as or higher than that above the tentorium. The latter feature probably accounts

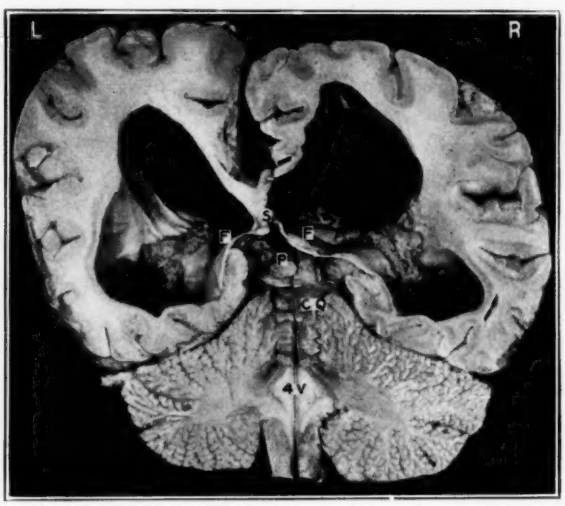


Fig. 4.—Photograph of a coronal section through a hydrocephalic brain, this section being taken through the splenium (*S*) to show the thinning which may occur in the crura of the fornix (*F*) (*F*), where they overlie the corpora quadrigemina and the pineal gland (*C Q* and *P*). The pulvinar of the thalamus is visible on the right side, below the fornix. From this section, it is easy to understand how rupture of the fornix may occur, followed by ventricular protrusion through the incisura tentorii behind and above the corpora quadrigemina.

for the infrequent occurrence of such protrusions into the cerebellar fossa. Usually when there is obstruction of the aqueduct of Sylvius, a tumor is present in this region which prevents such a herniation, certainly of such large size, from taking place. In our patient the tumor had at least partially blocked the third ventricle and had certainly blocked the aqueduct of Sylvius, as a result of its posterior extension. In the cases described by Peterson and Sweet the block was due to an infiltrating

neoplasm of small volume around the aqueduct, and as a result of this the pressure in the posterior fossa would tend to be less than the pressure above it.

Sweet coined a term "ventriculostium" to describe this type of cavity. So far, we have employed only the purely descriptive term "protrusions," but we prefer the term "diverticula" and have used it in the title of the article. It is a familiar term which conveys the idea of an extension outward from the cavity of the ventricle—similar to diverticula associated with other cavities in the body. As these protrusions are blind sacs not communicating with the subarachnoid space, the term "ostium" seems hardly appropriate.

It may be asked whether the protrusions ever produce symptoms or signs through pressure on adjacent structures. Sweet suggests this possibility in the discussion of his case, but it seems to us that in none of the cases reviewed were there any symptoms or signs which could not be explained by the position of the neoplasm itself and by the generalized increase in intracranial pressure. These protrusions undoubtedly develop slowly and therefore produce no symptoms. In this respect they may be contrasted with the acute herniation of the hippocampal gyrus through the incisura, which characteristically compresses the oculomotor nerve and rapidly produces pupillary changes.[5]

Differential Diagnosis.—There are several other types of cysts or cavities which may develop in the same region and which should be differentiated clearly from the "diverticula" just described.

1. Protrusion of the posterior wall of the third ventricle occurs frequently, when there is a block in the aqueduct or at some lower point in the cerebrospinal fluid pathway and dilatation of the third and lateral ventricles has taken place. The protrusion may develop from the suprapineal recess or below the pineal gland, in the space immediately above the posterior commissure. In one brain we examined the protrusion seemed to have occurred through the roof of the aqueduct itself, close to the third ventricle. In each case we have encountered in which the condition was well developed the protrusion passed through the incisura tentorii and the cavity lay above the lamina quadrigemina, within the subarachnoid space, occupying almost exactly the same region as the diverticula from the lateral ventricles which we have described, but in no case has it been so large. It seems as though the one type of protrusion must prevent the formation of the other, so that it would be surprising if the two types ever occurred together in the same brain.

5. Reid, W. L., and Cone, W. V.: Mechanism of Fixed Dilatation of Pupil Resulting from Ipsilateral Cerebral Compression, J. A. M. A. **112**:2030-2034 (May 20) 1939.

In pneumograms the continuity of the protrusions with the shadow of the posterior part of the third ventricle is usually clear if there has been adequate filling.

2. A dilated fourth ventricle when displaced upward may occupy the same general position as the diverticula from the lateral ventricles, but in pneumograms would only be liable to confusion when the ventricular system was incompletely filled, as happened in our case.

3. Cysts of the septum pellucidum, including the type described by Verga and others,[6] always lie above the tentorium and are bounded above by the corpus callosum and behind and below by the fornix. They should not be confused, either in pneumograms or in pathologic specimens, with protrusions of the third or lateral ventricles.

SUMMARY

A case is reported in detail and similar cases are described to illustrate that in rare instances protrusions, or diverticula, of the lateral ventricles may develop and extend into the cerebellar fossa near the apex of the tentorium.

It is suggested that these diverticula are the result of long-continued high intracranial pressure, with resultant internal hydrocephalus, and the development of a weak point in the floor of the lateral ventricles overlying the incisura tentorii. Any large space-occupying lesion in the cerebellar fossa tends to keep the infratentorial pressure high and prevent the formation of such diverticula.

With the aid of ventriculograms these diverticula should be diagnosed with a fair degree of certainty, when one is aware of their occurrence; otherwise they may be confused with a posterior protrusion of an enlarged third ventricle, a displaced fourth ventricle or other abnormalities in this region.

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6. (*a*) Verga, A.: Su'l ventricolo della vôlta a tre pilastri, Gazz. med. ital. lomb. **2**:225 and 364, 1851. (*b*) Dandy, W. E.: Congenital Cerebral Cysts of the Cavum Septi Pellucidi and Cavum Vergae: Diagnosis and Treatment, Arch. Neurol. & Psychiat. **25**:44-66 (Jan.) 1931. (*c*) Pendergrass, E. P., and Hodes, P. J.: Dilatations of Cavum Septi Pellucidi and Cavum Vergae, Ann. Surg. **101**: 269-295 (Jan.) 1935.

LEUKOCYTOSIS DURING VARIOUS EMOTIONAL STATES

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Leukocytosis has been noted frequently in patients with affective disorders when no infectious process or structural changes could be found to account for it. Although this phenomenon has been reported by numerous observers and various hypotheses, such as dehydration, foci of infection and acidosis, have been suggested as causes, no adequate studies of these factors have heretofore been carried out. An important question that has not been adequately stressed is whether the leukocytosis is related to a specific disease entity or whether the increase in white cells is secondary to the emotion exhibited by the patient regardless of the type of mental disease. If the latter is true, it is especially desirable to note any correlation between the level of the white blood cell count and the intensity of the emotional response. In a given situation, well adjusted persons frequently exhibit emotional states, such as anxiety and fear, which differ only in duration and intensity from those seen in psychiatric patients. It is therefore advisable to evaluate the increase in the white blood cell count in all patients from the standpoint of the influence of the emotions in addition to the factors usually considered.

Lacking an adequate investigation of the various physiologic mechanisms that induce an increase in the white cell count, other workers have postulated the presence of a so-called toxic condition. Bowman and Raymond [1] undertook a statistical study of the white cell count in 1,196 cases of schizophrenia at the Boston Psychopathic Hospital and found that in roughly 50 per cent of their cases the white cell count was over 10,000 and in 11 per cent over 15,000. Fever, dehydration and obscure infections were considered possible causes, but

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1. Bowman, K. M., and Raymond, A. F.: Physical Findings in Schizophrenia, Am. J. Psychiat. **8**:901, 1929.

studies to prove these conclusions were not decisive. Fleming[2] postulated "the presence of an infective condition" in cases of both acute and chronic mental disease because of an increase in the immature forms of polymorphonuclears. He ascribed this to probable obscure sources of infection in the gallbladder, sinuses and intestines, but there were no physical or laboratory examinations to substantiate this formulation. Another statistical study was recently made by Kasanin,[3] who compared 100 psychiatric patients in whom the white cell count was over 15,000 with a similar number of mentally ill patients with counts below 10,000. Patients with leukocytosis showed more evidence of infections and metabolic disorders, more frequently had temperature rises over 100 F. and manifested greater variations in mood. He expressed the opinion that there was a possible correlation between the amount of activity and the elevation in the white cell count. The counts were not done under basal conditions, and the patients were not followed for sufficiently long periods.

Wittkower[4] utilized another approach to the problem by inducing hypnotic sleep and suggesting various emotions, such as joy, sorrow, rage and jealousy. These affective states often caused an increase of 2,000 to 5,000 cells in the white cell count. Other workers (Dobreff and Tomoff[5] and Mora, Amtman and Hoffman[6]) demonstrated a variable leukocytosis in some patients before operation and in students on days of examinations. However, many of the counts were not increased; most often the white blood cell level was within a range that might be considered normal, and the question arises whether many of the changes are statistically significant.

METHOD

In investigating the problem of leukocytosis in psychiatric patients at the Payne Whitney Clinic, it was felt that an attempt should be made to control the known physiologic factors which cause an increase in the number of white blood cells. Accordingly, efforts were made to establish conditions approximating basal states. The counts were taken before breakfast with the patient in bed whenever possible, although certain excited patients were active while in bed and others frequently got out of bed. However, an attempt was made to keep activity at a minimum.

2. Fleming, G. W. T. H.: Some Aspects of Leucocytosis Associated with Mental Disorder, J. Ment. Sc. **78**:129, 1932.

3. Kasanin, J.: Leucocytosis in Mental Disease, New England J. Med. **210**: 641, 1934.

4. Wittkower, E.: Ueber affektive-somatische Veränderungen; die Affektleukocytose, Klin. Wchnschr. **8**:1082, 1929.

5. Dobreff, M., and Tomoff, W.: Durch Angst hervorgerufene somatische Veränderungen, Ztschr. f. d. ges. exper. Med. **84**:695, 1932.

6. Mora, J. M.; Amtman, L. E., and Hoffman, S. J.: Effects of Mental and Emotional States on the Leukocyte Count, J. A. M. A. **86**:945 (March 27) 1926.

The pulse rate was taken at the time of the count, and any unusual behavior was recorded. Each patient had a careful physical and neurologic examination by the resident staff and, in addition, was seen by an otolaryngologist, an ophthalmologist and a medical consultant. All women were examined by a gynecologist. A special technician, trained in working with psychiatric patients, was assigned to the investigation, and her technic was studied to eliminate all possible sources of error. Standardized pipets and a rotary shaker, as recommended by Bryan and Garrey,[7] were used. The capillaries in the finger were dilated by briskly rubbing the finger; deep stabs were made, and only sufficient pressure to open the wound was used. Occasional checks with venous blood showed no great difference, and this was almost always less than 800 cells per cubic millimeter. Special precautions were also observed in filling the counting chamber, and both sides of the chamber were counted, making a total of ten squares. Any other laboratory examinations which seemed indicated were performed concomitantly. In all patients, the sedimentation rate was estimated to aid in detecting the presence of possible infection. The carbon dioxide–combining power was determined to denote the presence of acidosis, the nonprotein nitrogen to evaluate deficiency in renal function, the specific gravity of the plasma to indicate dehydration and the fasting blood sugar to establish emotional influences on the epinephrine factor. The specific gravity was determined by the falling drop method and was used to follow changes in blood concentration over short periods. In certain selected cases, an investigation was made of the effect on the blood count of such drugs as barbital and sodium amytal.

All the patients were under continuous psychiatric observation, with careful attention given to psychologic, psychopathologic and general biologic behavior (activity; food intake; bowel activity; sleep; weight; pulse; menstruation; sexual activities). Through the study of the patient's personality, the physician was able to understand the reactions to the experimental situation of having the blood taken. The objective observation of behavior during the twenty-four hour period and the subjective descriptions of the patients in casual remarks as well as in medical interviews were evaluated carefully. The illness as a major reaction, the special phase of the illness which the patient was undergoing at the time of the blood study and whatever psychopathologic reactions occurred were taken into consideration. Special attention was paid to emotional reactions in the setting of the general psychopathologic picture. These emotional reactions were observed during the taking of the blood. They were later investigated in psychiatric interviews and finally correlated with the laboratory results.

The reliability of the technic is reflected in the fact that twenty counts made from the same sample of blood gave a mean of 8,958 cells per cubic millimeter, with a high of 9,500 cells and a low of 8,420. The standard error of the mean was ± 61.30. Statisticians ordinarily consider a mean to be reliable when the standard error of the mean is one third of, or less than, the mean. With our method the standard error of the mean was considerably less than one third of the mean. The standard deviation obtained was ± 274 cells, as compared with deviations of ± 227 and ± 255 cells obtained by Ponder, Saslow and Schweizer,[8] who used a careful technic of counting both sides of two counting chambers.

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7. Bryan, W. R., and Garrey, W. E.: Mechanical Device that Produces Uniform Dispersion of Blood Cells in Diluting Pipet, J. A. M. A. **103**:1059 (Oct. 6) 1934.

8. Ponder, E.; Saslow, G., and Schweizer, M.: On Variations in the White Cell Count of Man, Quart. J. Exper. Physiol. **21**:21, 1932.

On the basis of these figures, one is justified in concluding that with our method a variation of 820 cells or more, which is three times the standard deviation, is almost certainly due to causes other than chance errors in the measuring technic at this level. Another measure of the reliability of the technic is shown by the experiment in which duplicate counts on 25 patients were correlated and yielded a coefficient of reliability of 0.975, as compared with a theoretic maximum of 1.0.

In the evaluation of the significance of changes in blood counts the usual diurnal variation must be considered. Sabin, Cunningham, Doan and Kindwall [9] observed large fluctuations in the total white cell count of normal subjects during the twenty-four hour period. However, Ponder and his co-workers attributed the magnitude of these changes to faulty distribution of the small number of cells counted in the chamber. They expressed the belief that had larger numbers been counted the fluctuations would have been much smaller. For example, when only one side of a counting chamber was counted, that is, approximately 200 cells for a normal count, they found coefficients of variation from 7.7 to 13.5. When four sides were counted, the coefficients of variation ranged from 2.3 to 6.7. Thus a variation of 6,500 to 10,000 cells per cubic millimeter, observed in a patient over a period of three and one-half hours, by counting only one side of a chamber, could be reduced to a range of 8,000 to 9,000 cells when four sides were counted. However, no matter how many cells were counted, there remained a small "residual fluctuation," which probably represents an actual fluctuation in the blood count.

In psychiatric patients the observed changes were usually much greater than those noted in normal persons. Furthermore, the changes have added significance because of the abnormally high levels at which they occur. For example a change of 3,000 cells from 10,000 to 13,000 cells per cubic millimeter is certainly much more unusual in healthy, well adjusted persons than a change from 7,000 to 10,000 cells.

OBSERVATIONS

In a study of 200 patients representing consecutive admissions to the Payne Whitney Clinic, it was noted that approximately one third of the patients had initial white blood cell counts of 10,000 cells per cubic millimeter or over. Of the whole group, 34 patients had infectious diseases which probably influenced the blood picture. Infections of the upper respiratory tract, including chronic sinusitis, nasopharyngitis and rhinitis, were the most frequent infectious diseases. Other illnesses included pyelitis, pelvic inflammatory disease, pulmonary tuberculosis and localized abscess. Of this group of patients with infections, 19 patients had initial cell counts below 10,000 and 15 patients had counts over 10,000. In other words, evidence of infection could be shown in only 14 per cent of all patients with counts below 10,000 and in only 22 per cent of the patients with leukocyte levels over 10,000. Although the incidence of infection was greater in the group of patients with elevated white cell counts, 78 per cent of all subjects in this group had no infection that could be demonstrated. Table 1 shows a more detailed consideration of the aforementioned findings.

9. Sabin, F. R.; Cunningham, R. S.; Doan, C. A., and Kindwall, J. A.: The Normal Rhythm of the White Blood Cells, Bull. Johns Hopkins Hosp. **37**:14, 1925.

The sedimentation rate, as determined by the method of Rourke and Ernstene,[10] frequently was independent of the changes in the white cell count. Of the entire group of 200 patients, 42 had rates over 0.40 mm. per minute. Of these, only 19 had white cell counts over 10,000, and the rest had normal counts. Sixty-seven patients had counts over 10,000, and of these, 48 had normal sedimentation rates. In some of the patients suffering from panic reactions or excitement with anxiety, leukocytosis was accompanied by a high blood sugar value. In other patients, a decrease in sugar level accompanied the decreasing leukocytosis. On the other hand, some patients with subacute anxiety showed normal blood sugar which did not change with the change in the leukocyte level.

In the course of our studies it became apparent that there was no definite correlation between the level of the white cell count and specific

TABLE 1.—*White Blood Cell Levels for Two Hundred Psychiatric Patients*

	Percentage
Initial white blood cell counts over 10,000 *	33.5
10,000–12,000 cells	18.5
12,000–15,000 cells	12.5
15,000 cells or over	2.5
	Patients
Number in total series with infections	34
Number with infections and cell counts below 10,000	19
Number with infections and cell counts over 10,000	15
	Percentage
Incidence of infections in group with counts below 10,000	14
Incidence of infections in group with counts over 10,000	22

* In the entire series of 200 patients 26 per cent had white blood cell counts over 10,000 despite the absence of infection.

psychiatric disease entities. However, in certain patients with leukocytosis the degrees of elevation of the white cell count were often related to the intensity of the emotion. This relation was usually consistent in the same subject, but varied from patient to patient. The specific behavior most frequently associated with leukocytosis was panic reaction, depression with agitation, excitement with overactivity and anxiety and excitement with overactivity and elation. Improvement in the emotional reactions, either spontaneous or induced by medication, was associated with the return of the leukocyte count to normal levels.

The term "panic" as used in this paper is a sudden, excessive fear reaction in a setting of prolonged tension, characterized by extreme insecurity. Suspiciousness and persecutory delusions occur in stages of pronounced panic. Fear is differentiated from anxiety by the fact that

10. Rourke, M. D., and Ernstene, A. C.: A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in the Cell Volume Percentage of Blood, J. Clin. Investigation **8**:545, 1930.

the former has a definite content as compared with the feeling of impending disaster coming from within noted in anxiety reactions. Agitation occurs most often in depressed persons who are anxious or fearful. These patients display restlessness, with more or less incessant limited activity, such as wringing their hands, picking at their nails or other parts of the body and groaning. The behavioristic psychopathologic

TABLE 2.—*Correlation of Results of Blood Studies and Clinical Psychiatric Condition of Patients with an Initial White Cell Count Over 14,000 per Cubic Millimeter*

Case No.	Date	Leading Psychopathologic Symptoms	White Blood Cells	Adult Polymorphonuclears, %	Band Forms, %	Red Blood Cells, Millions	Hemoglobin, %	Hematocrit Reading, Mm.	Corrected Sedimentation Rate, Mm. per Min.
1711	1/15	Panic; paranoid ideas	16,300	44	7	4.84	100	48	0.15
	2/10	Suspicious; quiet; less tense	8,600	51	3				
1789	5/10	Panic; paranoid state	15,000	69	2	4.96	103		
	6/11	Friendly; tense	9,500	70	0				
1871	8/20	Panic; homosexual fears	17,300	69	4	5.50	108	51	0.43
	9/23	Fearful; agitated	10,900	70	2	5.55	108	47	0.26
	9/28	Moderately anxious; quieter	8,100	..	..	5.20	108		
1809	6/ 3	Excited; overactive; negativistic	15,350	78	1	4.74	96	46	1.20
	6/20	Less active; persistent delusions	10,300	63	0	5.64	100		
1739	3/ 5	Excited; fearful; assaultive	18,000	84	3	4.78	96	43	0.75
	3/12	Fearful; less active	14,750	79	1	4.52	89		
1723	2/ 6	Excited; negativistic; fearful	14,300	83	2	4.90	96	45	0.17
	2/13	Impulsive; negativistic; cellulitis	21,000	82	2				
	2/24	Mute; tube fed; hallucinations	11,500	69	3				
	3/ 4	Quieter; less active; sodium amytal	10,400	62	4				
1907	10/25	Agitated; marked fear; depressed	16,600	72	0	5.40	109	50	0.23
	11/ 1	Less agitated; moans constantly	11,450	73	2	4.90	94	47	0.27
	11/18	More agitated despite barbital	16,000	82	0				
	12/ 3	Quieter; anxious; depressed	9,300	67	2				
	12/20	More at ease; still anxious	6,200	66	1	....	...	45	0.16
	2/11	Mildly agitated; depressed	13,700	..	..	....	...	46	0.28
1724	2/ 5	Anxious; tense; depressed	14,600	65	2	5.18	107	46	0.25
	2/ 8	Anxious; less depressed	16,700	72	3				
	2/19	Anxious; resentful; sad	17,000	77	2				
1714	1/15	Tense; anxious; resentful	14,200	68	7	4.48	96	42	0.29
	4/24	Anxious; irritable	12,700	75	2				
	9/12	Anxious about dental operation	16,100	69	7	5.06	96		
	10/29	Resentful of mother; anxious	17,900	71	4				
	11/12	Anxious; hypochondriacal	11,100	63	4	....	...	41	0.26

symptoms are amplified by the patients' descriptions of their emotions and preoccupations. In patients who display excitement it is difficult to study the effects of each symptom separately. Consequently, both reactions (overactivity and emotions) were considered together in their effect on the leukocyte count.

Table 2 shows a correlation of the results of blood studies and the clinical psychiatric condition of patients with an initial white cell count over 14,000 cells per cubic millimeter. These data demonstrate char-

acteristic reactions noted in our subjects and represent only a few of the total number of counts taken in this group. Three patients were omitted from the table—2 because of somatic disease that complicated the picture and 1 because of insufficient studies.

The first 3 cases in table 2 were those of patients who experienced about the time of admission incidental panic reactions of a marked degree, as indicated by paranoid ideas. In all 3 cases the count returned to a normal level when the marked fear subsided and the patient felt more secure in the hospital environment. The psychiatric illness was different in each case, but the psychopathologic symptoms were similar. The fourth, fifth and sixth cases in the table were those of patients with excitement characterized by overactivity and fear, representing a less marked degree of fear. These patients showed a great deal of impulsiveness and negativism. The agitated patient (case 1907) showed a definite correlation between the intensity of agitation (anxiety) and the white cell count. During the quieter periods, when the white cell count was within normal limits, the patient was able to feed herself with only little assistance. When she again became more agitated, her white cell count rose and tube feedings had to be resumed. The 2 patients with marked anxiety reactions (cases 1724 and 1714) showed a similar correlation between the white cell count and the intensity of the emotional reaction. With the last patient resentment was usually a more important factor than anxiety. In contrast to the aforementioned positive observations, no definite consistent relation was noted between the degree of leukocytosis and the red blood cell count, the hemoglobin content, the corrected sedimentation rate or the percentage of adult polymorphonuclears or band forms.

More detailed observations on 1 of these patients (case 1907) are presented in figure 1. It is readily noted that the peaks, or highest degrees, of leukocytosis occurred concomitantly with a panic reaction. At first, the administration of barbital in small doses through the day succeeded in diminishing the patient's fear, as seen objectively in his appearance and behavior, in the decreased average pulse rate and in some improvement in sleep. Subjectively, he expressed fear less frequently and with less intensity. When the administration of the drug was interrupted, he became more agitated, and another acute panic occurred, which again was associated with a marked elevation of the white cell count and an increase in pulse rate. The intensity of the emotional reaction gradually subsided when the drug was again given, but after a period of about three and a half months a tolerance for the drug appeared to have been established. Even though the dose was unchanged, the patient again became more fearful, and when subsequent

panic reactions occurred, the white cell count again rose, although not to as high a level as formerly. These observations are significant in that they demonstrate the relation of the white cell count to the psychopathologic emotional reaction rather than to the dose of sedative administered. Inspection of the data in figure 1 shows a lack of correlation of the leukocyte level with the specific gravity of the plasma or the red blood cell count.

The leukocytosis observed in patients with marked emotional reactions is most likely due to a redistribution of the white cells in the blood stream. In practically all our subjects either there was no significant change in the differential count or the changes were obviously not cor-

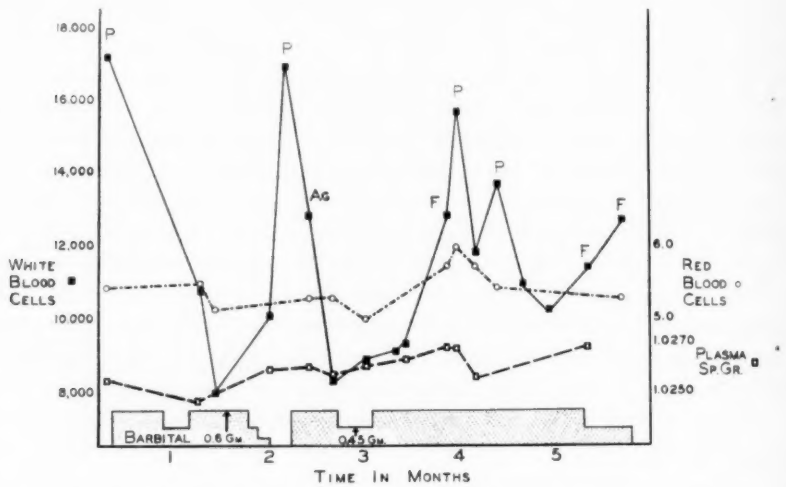

Fig. 1 (case 1871).—Effect of panic reactions on the white blood cell count. The white blood cell counts are represented by the solid rectangles, with the values listed on the left ordinate. The red blood cell counts are shown by circles and the plasma specific gravities by the outlined rectangles, with their respective values on the right ordinate. The letters *P*, *Ag* and *F* represent panic, agitation and fear, respectively.

related with the height of the white cell count. A typical instance is shown in figure 2, in which, after the rapid withdrawal of barbital, the patient showed fear of panic intensity. Associated with the emotional state there was a sharp rise in the total white cell count but no significant change in the differential count. The percentage of adult polymorphonuclears and of band forms continued at the same levels during the phase of pronounced leukocytosis and even after the white cell count had returned to a normal level. The changes in the white cell count could

not have been related to any increase in activity, since the patient continued to be active to a similar degree even after the panic reaction had subsided.

These changes in the emotional status and in the leukocyte levels induced by a barbiturate are demonstrated more acutely when the drug is given by vein. In a series of nineteen experiments on 14 patients, sodium amytal, in doses ranging from 0.3 to 0.5 Gm., was injected intravenously. The drug was given until definite clinical effects, such as nystagmus or slurring of speech, occurred. Most often this required

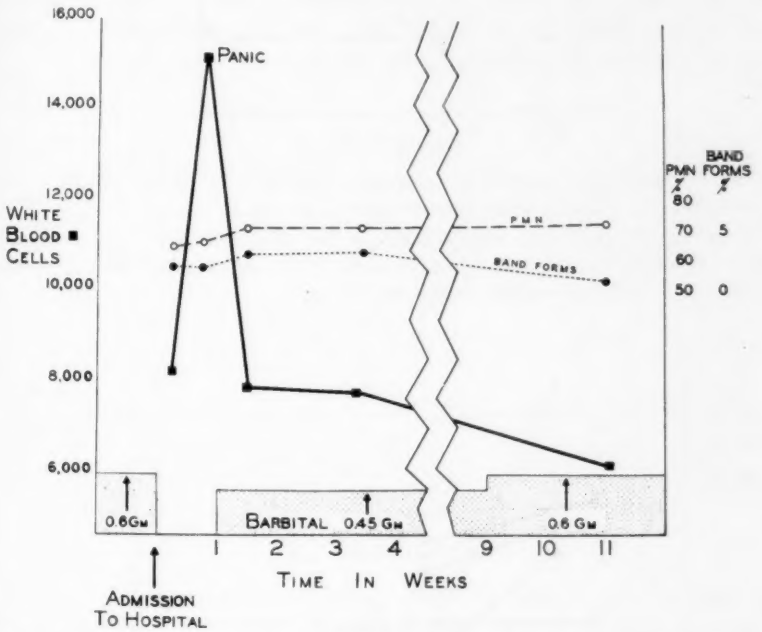

Fig. 2 (case 1980).—Lack of change in the differential count during panic reaction.

The solid and the open circles represent band forms and adult forms of polymorphonuclears, respectively. The solid rectangles show the heights of the white blood cell count. The dose of barbital administered is shown at the bottom of the figure. When the drug was suddenly stopped, the patient soon became more fearful and experienced a panic reaction. The zigzag lines signify a lapse of about four weeks.

0.5 Gm. of sodium amytal. The results can be summarized by saying that the drug induced striking reductions in elevated leukocyte counts when there were accompanying favorable changes in the emotional status. While there also was often a small reduction in the specific gravity of the plasma, this occurred independently of the changes in the white cell

count and was of such a magnitude as not to enable one to explain the reduction in white cells on a basis of dilution.

Figure 3 shows a characteristic reaction to the intravenous injection of sodium amytal in a patient who displayed marked anxiety. The count taken under basal conditions with the patient in bed was about 13,600

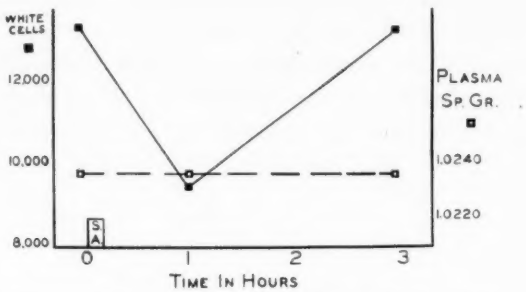

Fig. 3 (case 1866).—Effect of intravenous injection of sodium amytal on the white blood cell count and the plasma specific gravity.

White blood cell counts are indicated by the solid rectangles and the plasma specific gravities by the outlined rectangles. *S.A.* shows when the intravenous injection of 0.5 Gm. of sodium amytal was given.

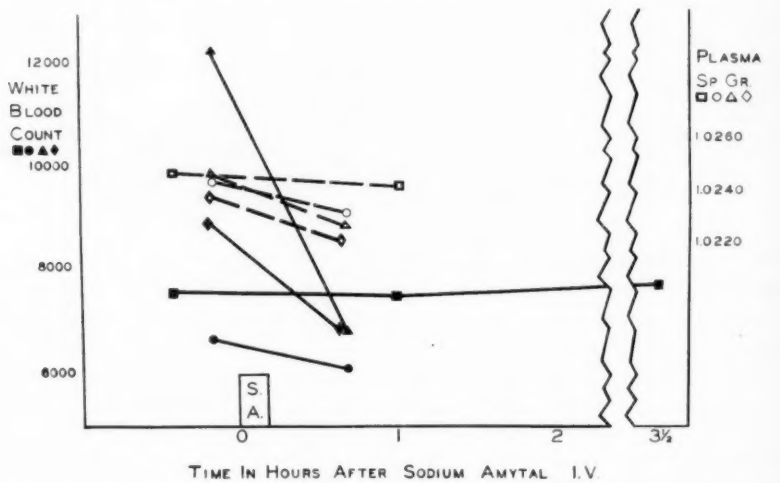

Fig. 4 (case 1941).—Effect of intravenous injection of sodium amytal on the white blood cell count at different initial levels.

The series of injections of sodium amytal were performed on the same patient on different occasions. The solid geometric forms represent the heights of the white blood cell count, and the same geometric form in outline shows the plasma specific gravity taken at the same time as the corresponding blood count; for example, the solid rectangles represent the white cell count and the rectangles in outline show the specific gravity as determined from the same blood sample.

cells per cubic millimeter and after the injection of the drug fell to within normal limits. The fall was associated with a noticeable decrease in anxiety, and the patient began to talk quite easily about his personal affairs. As the effect wore off, his tense feeling slowly returned, he talked less freely and his muscles were less relaxed. The white cell count also returned to its previous level. The plasma specific gravity showed no corresponding change.

A further demonstration of the effect of sodium amytal was shown by a series of injections on the same patient at times when he was agitated and again when he was less restless. Figure 4 shows the results in such a series of experiments. The highest initial count was obtained when the patient was most agitated and the lower counts when he was

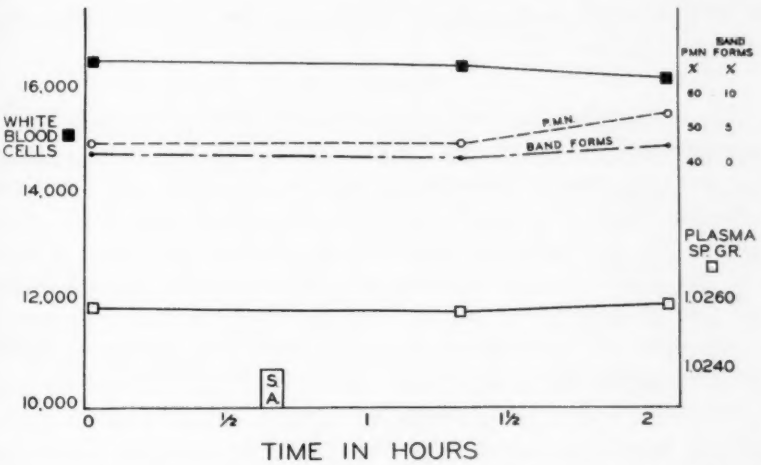

Fig. 5 (case F-2).—Effect of sodium amytal on leukocytosis which is not of emotional origin.

Sodium amytal was administered intravenously to a patient with leukocytosis due to dermatomyositis. The solid rectangles signify white blood cell count levels. The adult and band forms of polymorphonuclears are represented, respectively, by open circles and by solid dots connected by broken lines. The open rectangles denote the plasma specific gravity. *S.A.* shows the time of the injection of sodium amytal.

less so. When the initial white cell count was elevated, sodium amytal induced striking reductions in the leukocyte level; on the other hand, when the white cell count was within normal limits the drug had relatively little effect. There was a concomitant reduction in the plasma specific gravity, but this was definitely not in proportion to the decrease in the white cell count. The medication resulted in a decrease of muscle tension and of agitation, indicating decreased anxiety. The patient was more relaxed and was able to talk more freely. When agitated, the

patient stammered and grunted, without being able to make himself understood, but after the injection he spoke with relative ease.

A similar experiment was performed on a patient with dermatomyositis who had a high white cell count, due to her illness. She was selected because she was a placid type of person who showed little anxiety, yet had a marked leukocytosis. Sodium amytal was given to the point where the patient had definite nystagmus and slurring of speech; yet the count was not materially affected by the drug. The differential count and the specific gravity of the plasma showed no significant changes (fig. 5).

The intravenous administration of sodium amytal to a few patients with agitation who showed no elevation in the white cell count was not attended by any further reduction in the leukocyte level, even though the drug caused a decrease in the intensity of the particular emotion.

COMMENT

The leukocytosis observed in various emotional states appeared to be intimately related to the psychopathologic emotion. As the patients improved, the general tendency was for the white cell count to return to the usual level. In the present series of patients, acidosis, as determined by the carbon dioxide–combining power, was of infrequent occurrence and did not appear to play a role in the causation of leukocytosis. The claim that dehydration was a frequent cause of leukocytosis was not supported by our findings. Clinically the great majority of patients with leukocytosis did not show signs of anhydremia. The specific gravity of the urine, the hematocrit reading and plasma specific gravity likewise militated against the blood concentration as the cause of the elevated white cell count.

A significant fact noted was that the differential count did not show any definite and consistent shift to the left when the total white cell count was elevated by emotional factors. Marked changes in the total white cell count over a short period, as in the experiments with sodium amytal, also did not cause any significant changes in the differential count. It thus appears likely that the leukocytosis observed in our subjects was due to a redistribution of white blood cells from so-called organ reservoirs, such as collapsed capillaries in the muscles at rest, the spleen, the liver and the lungs. Leukocytic skimming and accumulation in capillaries of various organs have been observed directly by other workers, and it is probable that the circulatory changes induced by emotional reactions wash out these sequestered cells into the peripheral blood stream. The effect of the emotions on the physiologic processes most probably is mediated by the autonomic nervous system. This con-

tention might be supported by the fact that epinephrine injected parenterally has been shown to produce leukocytosis, especially in persons who are of an anxious and worrisome makeup.[11]

The mode of action of sodium amytal in lowering the white cell count might be explained by a reversal of the processes causing leukocytosis. Searles [12] recently noted that sodium amytal given to dogs in anesthetic doses caused dilatation of the spleen, with a corresponding decrease in the hematocritic reading. However, this alone would not suffice to explain the decrease in white cell counts in view of the much greater reduction in the white cells as compared with the red cells. The recent studies of Ebert and Stead [13] indicate that while there is an abundance of evidence that the spleen serves as a reservoir of red blood cells in certain species, such as the dog, cat and horse, reservoirs of this nature do not exist in the normal human subject.

CONCLUSIONS

Leukocytosis is of frequent occurrence in patients with emotional disorders. Most of these patients show no infectious process or structural changes to account for the elevated white blood cell count. Briefly, the observations on 200 psychiatric patients were as follows: There was no definite correlation between the level of the white cell count and the specific psychiatric disease entity. On the other hand, in certain patients with an elevated white cell count the degree of leukocytosis was often related to the intensity of the psychopathologic emotion. This relation was consistent in the same subject but varied from patient to patient. The emotional reactions associated with leukocytosis were fear and panic reactions, depression with anxiety (agitation), subacute and persistent anxiety states, persistent intense resentment and excitements which were characterized by overactivity with fear and anxiety or with elation and anger. Leukocytosis was not observed in any cases of sadness without anxiety or of elation without anger. Leukocytosis cannot be explained solely by the emotional factor. In 1 case in which there was marked anxiety a low white cell count was persistently found. Improvement in the emotional reactions, either spontaneous or induced by sedation, was associated with the return of the leukocyte count to normal levels.

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11. McLeod, J. P. U., and Highsmith, J. D.: Effect of Fear on Diagnosis, M. Rec. **153**:9, 1941.

12. Searles, P. W.: Effect of Certain Anesthetics on Blood, J. A. M. A. **113**: 906 (Sept. 2) 1939.

13. Ebert, R. V., and Stead, E. A., Jr.: Demonstration That in Normal Man No Reserves of Blood Are Mobilized by Exercise, Epinephrine, and Hemorrhage, Am. J. M. Sc. **201**:655, 1941.

The intravenous administration of sodium amytal induced striking reductions in elevated leukocyte counts when there were accompanying favorable changes in the emotional status. The specific gravity of the blood plasma often varied in patients with leukocytosis, and it usually was reduced by intravenous injection of sodium amytal; however, changes in the white cell count and the plasma specific gravity occurred independently of each other. Alterations in the sedimentation rate were frequently independent of changes in the white cell count. Similarly, a lack of correlation between the blood sugar level and the white cell count was often observed, although high blood sugar values were frequently found in patients with marked panic and with excitement accompanied by great anxiety.

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INTRACRANIAL BLOOD FLOW IN DEMENTIA PARALYTICA, CEREBRAL ATROPHY AND SCHIZOPHRENIA

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CINCINNATI

Recently an objective method for measuring a function of total intracranial blood flow has been developed,[1] which seems suitable for comparing the blood flow of groups of subjects. The following report is a comparative study of the total intracranial blood flow, as determined by this method, of patients suffering from dementia paralytica, from nonsyphilitic cortical atrophy and from schizophrenia. A group of 18 patients in the hospital who exhibited no clinical evidence of abnormal circulation in the brain or elsewhere served as controls.

METHOD

The method has been described in detail.[1] The relative intracranial blood flow was estimated by measuring the rate of cerebrospinal fluid displacement through a large lumbar puncture needle during sudden temporary compression of the veins of the neck. The studies were carried out with the cerebrospinal fluid pressure adjusted to 200 mm. of fluid. The veins were compressed by inflation of a freely distensible cuff which was bound around the neck. Under these circumstances, the rate of outflow of cerebrospinal fluid during compression of the veins is a function of the rate of inflow of arterial blood into the cranium. In order to obtain values comparable in different persons, the readings were obtained by utilizing an occlusive pressure sufficient to cause maximum rates of cerebrospinal fluid displacement for each subject. This cuff pressure varied from 60 to 70 mm. of mercury. The relative intracranial blood flow for each subject was calculated by averaging a series of five to thirty cerebrospinal fluid displacement curves. All determinations were carried out during periods when the subjects were comfortable and relaxed.

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1. Ferris, E. B., Jr.: Objective Measurement of Relative Intracranial Blood Flow in Man, with Observations Concerning the Hydrodynamics of the Craniovertebral System, Arch. Neurol. & Psychiat. **46**:377 (Sept.) 1941.

RESULTS

Control Group.—Table 1 shows the results for 18 subjects chosen as controls. These were patients residing in the hospital who were convalescing from or under observation for various disorders. They presented no significant mental abnormalities. Although relatively few of these persons could be considered to be "normal," it was felt that they served as a reasonably good control group under the circumstances, which required that there be a diagnostic or therapeutic indication for the lumbar puncture.

TABLE 1.—*Data on Control Subjects*

No.	Name	Age, Yr.	Sex	Race *	Weight, Lb.	Diagnosis	Average Cerebrospinal Fluid Displacement Rate Cc. per Min.
1	C. J.	48	M	C	112	Syphilitic aortitis	115
2	J. C.	40	F	C	150	Acute gastroenteritis; hypertension; hypertrophic arthritis	142
3	M. D.	43	F	C	112	Bronchial asthma	117
4	M. H.	50	F	C	117	Epigastric hernia	149
5	L. P.	48	M	C	130	Alcoholic peripheral neuritis	129
6	L. K.	44	M	W	150	Tabes dorsalis with optic atrophy	143
7	A. R.	47	M	C	112	Ulcer of stomach; syphilitic aortitis	124
8	L. W.	53	M	C	140	Subacute combined system disease and pernicious anemia	117
9	E. T.	35	M	C	100	Alcoholic peripheral neuritis	170
10	G. B.	35	M	W	115	Birth injury with spastic hemiplegia	138
11	C. K.	56	M	W	120	Tabes dorsalis	148
12	J. H.	40	M	W	180	Chronic alcoholism; asymptomatic syphilis of central nervous system	120
13	T. N.	34	M	W	140	Chronic alcoholism	124
14	J. P.	46	M	C	134	Tabes dorsalis with optic nerve atrophy	105
15	G. M.	29	M	W	140	Postencephalitic parkinsonism	132
16	H. W.	41	M	W	163	Chronic alcoholism; delirium tremens	111
17	C. H.	42	M	W	131	Chronic alcoholism	141
18	C. R.	44	M	W	150	Chronic alcoholism	140
	Average						131

* In this table and in the accompanying tables, C means Negro and W white.

The average flow [2] for this control group was 131 cc. per minute, with individual variations ranging from 105 to 170 cc. per minute (table 1).

Dementia Paralytica.—Twenty-seven patients constituted this group. As determined by routine mental examinations, 12 were considered to be mildly demented (table 2) and 15 to be severely demented (table 3). The average duration of symptomatic illness was one and one-tenth years for the mildly demented group and three and two-tenths years for the severely demented group.

2. The values for the intracranial blood flow as used throughout this paper represent the cerebrospinal fluid displacement rate, which is not the actual total intracranial blood flow, but only a reasonably constant function of it.

TABLE 2.—*Data on Patients with Dementia Paralytica (Mild Dementia)*

No.	Name	Age, Yr.	Sex	Race	Weight, Lb.	Duration of Illness	Treatment	Outcome	Average Cerebrospinal Fluid Displacement Rate, Cc. per Min.
1	F. G.	39	F	W	99	7 yr.	Malaria and chemotherapy	No improvement	156
2	L. D.	42	F	W	110	1 wk.	Malaria	Improvement	138
3	H. G.	36	M	W	148	4 mo.	Typhoid	Improvement	156
4	P. W.	51	M	C	112	4 mo.	Chemotherapy	Improvement	114
5	R. J.	65	M	C	143	1 yr.	Chemotherapy	Improvement	133
6	S. H.	34	M	W	140	3 mo.	Malaria	Death	117
7	C. L.	41	M	W	130	2 yr.	Malaria (1938) (relapse [1939])	Improvement	93
8	H. L.*	28	F	W	95	3 yr.	Malaria and chemotherapy	Improvement	133
9	F. W.*	54	M	W	145	7 yr.	Chemotherapy	Slight improvement	126
10	E. E.*	46	F	W	115	?	Chemotherapy	No improvement	116
11	J. H.	40	M	W	?	1 yr.	Diathermy	No improvement	150
12	R. T.	39	M	W	105	5 mo.	Malaria and chemotherapy	Improvement	122
	Average								129

* State Hospital patient.

TABLE 3.—*Data on Patients with Dementia Paralytica (Moderate to Severe Dementia)*

No.	Name	Age, Yr.	Sex	Race	Weight, Lb.	Duration of Illness	Treatment	Result	Average Cerebrospinal Fluid Displacement Rate, Cc. per Min.
13	W. A.	55	M	W	120	6 mo.	Malaria	No improvement	86
14	W. M.	60	M	C	120	?	Chemotherapy	Death	116
15	L. C.	40	M	C	120	1 yr.	Malaria	Improvement	96
16	E. S.	39	M	W	120	1 wk.	Malaria and chemotherapy	Improvement	81
17	F. W.	51	M	C	114	4 mo.	Chemotherapy	No improvement	93
18	L. B.	48	M	W	158	6 mo.	Malaria	No improvement	136
19	M. C.	45	F	W	105	8 yr.	Malaria	No improvement	115
20	C. L.	42	M	C	150	7 yr.	Chemotherapy and fever	No improvement	62
21	A. C.	39	F	W	96	1 yr.	Malaria	No improvement	77
22	G. M.	39	M	W	109	2 yr.	Malaria	Improvement	125
23	H. D.*	40	M	W	195	7 yr.	Malaria and chemotherapy	No improvement	144
24	L. B.*	52	F	W	85	7 yr.	Malaria and chemotherapy	No improvement	63
25	W. D.*	42	F	W	115	3 yr.	Malaria and chemotherapy	No improvement	101
26	H. A.*	38	M	W	150	7 yr.	Malaria and chemotherapy	No improvement	88
27	R. B.*	45	F	W	115	5 yr.	Chemotherapy	No improvement	71
	Average								97

* State Hospital patient.

TABLE 4.—*Data on Patients with Cerebral Atrophy*

No.	Name	Age, Yr.	Sex	Weight, Lb.	Diagnosis	Duration of Illness	Outcome	Encephalographic Findings	Degree of Cerebral Atrophy	Degree of Dementia	Average Cerebrospinal Fluid Displacement Rate, Cc. per Min.
1	A. D.	16	F	98	Porencephaly, left occipital region; convulsions; mental deficiency	16 yr.	No improvement	Dilatation of left ventricle with large porencephalic cyst	Moderate	Marked	100
2	C. B.	53	M	140	Psychosis with cerebral arteriosclerosis and cortical atrophy	2 yr.	No improvement	Marked ventricular and subarachnoid dilatation	Marked	Marked	83
3	C. W.	38	M	100	Cortical atrophy (etiology ?)	2½ yr.	No improvement	Moderate ventricular dilatation and marked subarachnoid filling	Marked	Marked	71
4	M. J. L.	12	F	105	Convulsions; mental deficiency	9 yr.	No improvement	Slight ventricular dilatation	Slight	Marked	100
5	F. H.	52	M	175	Degenerative disease of cortex; Alzheimer's or Pick's disease (?)	3 yr.	No improvement	Generalized cerebral atrophy, most marked in left frontal lobe	Marked	Marked	116
6	C. W.	52	M	160	Cerebral atrophy; convulsions; hypertension	8 yr.	Improvement	Increased subarachnoid filling in frontal and parietal regions	Mild	None	121
7	A. B.	67	F	114	Cerebral arteriosclerosis with generalized cerebral atrophy	1½ yr.	Slight improvement	Moderate dilatation of ventricles and subarachnoid space	Moderate	Moderate	98
8	A. M.	48	F	150	Hyperostosis frontalis interna; convulsions	6 wk.	No improvement	Slight atrophy of frontal areas	Slight	None	122
										Average	101

The average flow for the entire group of patients with dementia paralytica was 111 cc. per minute, for the 12 mildly demented subjects 129 cc. per minute and for the 15 more severely demented subjects 97 cc. per minute. Although sufficient data are not available for an accurate statistical analysis, it appears evident from observing the individual values that the flow was significantly less for severely

TABLE 5.—*Data on Patients with Schizophrenia*

Number and Name	Age, Yr. and Sex	Weight, Lb.	Type of Schizophrenia	Duration of Illness	Psychomotor Activity	Outcome	Average Cerebrospinal Fluid Displacement Rate, Cc. per Min.
1 R. H.	18 M.	155	Simple	2 yr.	Decreased	Improvement (insulin)	87
2 J. A.	28 M	130	Hebephrenic	3 yr.	Normal	No improvement	141
3 H. R.	31 M	120	Paranoid	2 mo.	Decreased	No improvement (insulin)	115
4 J. W.	36 M	110	Paranoid	1 yr.	Increased	No improvement	135
5 F. R.	42 M	142	Paranoid	9 yr.	Normal	No improvement	127
6 W. T.	28 M	134	Paranoid	5 mo.	Decreased	No improvement	98
7 C. B.	18 M	127	Catatonic	3 mo.	Decreased	No improvement	99
8 H. C.	25 M	168	Paranoid	2 wk.	Normal	Improvement (insulin)	116
9 I. K.	25 F	100	Hebephrenic	3 mo.	Decreased	No improvement (insulin)	112
10 R. B.	36 M	182	Paranoid	3 yr.	Normal	No improvement (insulin)	96
11 M. L.	32 F	143	Hebephrenic	1 mo.	Decreased	Improvement (insulin)	126
12 G. R.	30 M	170	With mental deficiency	2 wk.	Increased	Slight improvement	162
13 E. R.*	29 M	112	With mental deficiency	1 yr.	Normal	No improvement	109
14 E. G.*	27 M	150	Hebephrenic	1 yr.	Normal	No improvement	127
15 R. S.*	31 M	163	Simple with mental deficiency	2 yr.	Decreased	No improvement	107
16 V. R.*	35 M	115	Paranoid	3 yr.	Decreased	No improvement	120
						Average	117

* State Hospital patient.

demented patients with dementia paralytica than for mildly demented patients with the disease or for the control subjects.

Nonsyphilitic Cerebral Atrophy.—This group consisted of 8 patients for each of whom the diagnosis of cerebral atrophy was made by means of air encephalograms or ventriculograms. From a study of the roentgenograms, the relative degree of atrophy was estimated in each subject by an independent observer. The average flow for the group was 101 cc. per minute (table 4). Inspection of the data indicated a tendency for the blood flow to be less in those subjects having marked

cortical atrophy than in those having slight to moderate atrophy, and for the flow for the entire group to be significantly less than that for the controls.

Schizophrenia.—This group comprised 15 patients who suffered from various types of schizophrenia (table 5). The average flow for this group was 117 cc. per minute, which, although lower than that for the control group (131 cc. per minute) is of doubtful significance because of the wide scattering of individual values (86 to 162 cc. per minute). No trend of correlation of the blood flow values with the type of schizophrenia, the duration of symptoms or the clinical outcome could be established. However, there appeared to be a suggestive tendency for the blood flow to be higher in patients exhibiting increased psychomotor activity.

COMMENT

In a comparative study of a function of the total intracranial blood flow of these groups, the only significant variation from the controls appeared in the more severely demented persons with dementia paralytica and in those with marked cortical atrophy of the nonsyphilitic type. Although we have no objective data on the subject, it is likely that the severely demented patients with dementia paralytica also had cortical atrophy, as it is a common pathologic finding in this disease. The most likely cause for the diminution in the total intracranial blood flow in these conditions is that there is less brain substance to be supplied with blood, and probably the total cross sectional area of the blood vessels of the brain is less than that in subjects with normal-sized brains. The latter assumption seems reasonable, for diseased blood vessels have been stated to be the primary cause of the symptoms and of the pathologic changes in dementia paralytica [3] and in the degenerative types of cortical atrophy. The fact should be stressed that the method which we have applied gives an index of the total intracranial blood flow and not of the flow per unit volume of brain substance. These studies suggest that the total intracranial blood flow is diminished in persons who have a pathologic diminution in brain volume, but that the blood flow per unit of brain substance may well be normal.

The cause of the somewhat low values obtained for certain of the schizophrenic patients is not clear. There is no evidence that the total volume of the brain is decreased in this condition. The individual range of blood flow within the group was pronounced, varying from 87 to 162 cc. per minute. The marked scattering of the values is in keeping with the pattern of the results of other physiologic studies of

3. Merritt, H. H.: Putnam, T. J., and Campbell, A. C. P.: Pathogenesis of the Cortical Atrophy Observed in Dementia Paralytica, Arch. Neurol. & Psychiat. **37**:75 (Jan.) 1937.

schizophrenia.[4] There was no correlation between the blood flow values and the type of schizophrenia, the duration of the illness, the severity of symptoms or the outcome. It is of interest that patients exhibiting decreased psychomotor activity tended to have a lower rate of blood flow than those exhibiting increased psychomotor activity.

SUMMARY

1. The average relative total intracranial blood flow was 131 cc. per minute for 18 control persons.

2. The average intracranial blood flow was 129 cc. per minute for 12 mildly demented and 97 cc. per minute for 15 severely demented patients with dementia paralytica.

3. The average intracranial blood flow was 101 cc. per minute for 8 persons with nonsyphilitic cortical atrophy. In this group there appeared to be a relation between the blood flow and the degree of cortical atrophy.

4. The average intracranial blood flow for 16 schizophrenic patients did not differ significantly from that for the control group; however, the values from person to person showed much greater scattering. There was a suggestive tendency for patients who exhibited increased psychomotor activity to have higher values than patients who exhibited decreased psychomotor activity.

Dr. Nathaniel Brower and Mrs. Jane K. Friedlander gave technical assistance.

4. McFarland, R. A., and Goldstein, H.: Review of the Biochemistry of Dementia Praecox, Am. J. Psychiat. **95**:509 (Nov.) 1938.

FACTOR OF HYPOXIA IN THE SHOCK THERAPIES OF SCHIZOPHRENIA

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Observations [1] on the physiologic changes occurring during the insulin treatment of schizophrenia have disclosed a diminished cerebral metabolism. Less oxygen is removed from each hundred cubic centimeters of blood passing through the brain, and the blood flow is somewhat diminished.[2] In other studies made on patients receiving the metrazol treatment decreased oxygen saturation of arterial hemoglobin during the treatment was noted.[3] This procedure, therefore, also causes decreased brain metabolism due not to an absence of sugar but to the lack of oxygen necessary to combine with dextrose. As a result of these observations another method was devised which also decreases cerebral metabolism.[4] The patients are subjected to short periods of nitrogen inhalation. Under these conditions, too, a fall in the saturation of arterial hemoglobin is observed.[5]

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1. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Biochemical Changes Occurring in the Cerebral Blood During the Insulin Treatment of Schizophrenia, J. Nerv. & Ment. Dis. **89**:273-293, 1939.

2. Himwich, H. E.; Bowman, K. M.; Daly, C.; Fazekas, J. F.; Wortis, J., and Goldfarb, W.: Cerebral Blood Flow and Brain Metabolism During Insulin Hypoglycemia, Am. J. Physiol. **132**:640-647, 1941.

3. Himwich, H. E.; Bowman, K. M.; Fazekas, J. F., and Orenstein, L. L.: Effect of Metrazol Convulsions on Brain Metabolism, Proc. Soc. Exper. Biol. & Med. **37**:359-361, 1937. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Metabolism of the Brain During Insulin and Metrazol Treatments of Schizophrenia, J. A. M. A. **112**:1572-1573 (April 22) 1939.

4. Alexander, F. A. D., and Himwich, H. E.: Nitrogen Inhalation Therapy for Schizophrenia, Am. J. Psychiat. **96**:643-655, 1939.

5. Himwich, H. E.; Alexander, F. A. D., and Lipetz, M.: Effect of Acute Anoxia by Breathing Nitrogen on the Course of Schizophrenia, Proc. Soc. Exper. Biol. & Med. **39**:367-369, 1938. Lipetz, B.: Preliminary Report on the Results of the Treatment of Schizophrenia by Nitrogen Inhalation, Psychiatric Quart. **14**:496-503, 1940.

Since the aforementioned studies have been published, the severity of the metrazol convulsions has been ameliorated by the use of parasympatheticolytic drugs, erythroidine [6] and curare.[7] Meanwhile, the electrical form of shock therapy was introduced in this country.[8] The object of this communication is to determine whether hypoxia is also associated with more recent forms of shock therapy.

METHOD

Most of the patients studied had a condition diagnosed as schizophrenia. They were receiving the modified metrazol and electrical shock therapies. The femoral artery was tapped at various times before, during and after the convulsive episode. The blood was analyzed by the method of Van Slyke and Neill [9] for its oxygen content and capacity; the hemoglobin saturation was calculated from these values.

TABLE 1.—*Effect of Metrazol Convulsions with Erythroidine*

Patient No.	Oxygen Content, Volume per Cent	Oxygen Capacity, Volume per Cent	Hemoglobin Saturation, Percentage	Time Blood Was Drawn in Relation to Convulsions
1	18.53	19.22	97	Before
	16.63	.....	86	After
2	13.87	16.08	86	After
3	11.36	16.60	69	During
	6.22	.....	38	Later
	8.85	.....	53	After
4	7.95	17.50	46	Clonic
	5.65	.....	32	Clonic
5	11.30	15.25	74	Tonic
	4.55	.....	30	Clonic
	1.96	.....	13	Posteonvulsive apnea
6	1.68	16.40	10	Posteonvulsive apnea
	0.72	.....	4	Posteonvulsive apnea
7	0.37	16.96	2	Posteonvulsive apnea
	3.58	.....	22	Immediately after prostigmine

In the study of the effect of cyanide on brain metabolism dogs were used, samples of blood being collected from the femoral artery and from the superior longitudinal sinus.

RESULTS

Table 1 presents the results of the analyses of blood collected from patients with schizophrenia who received metrazol wtih beta erythroidine hydrochloride. It may be seen that before these drugs were used the

6. Rosen, S. R.; Cameron, D. E., and Ziegler, J. B.: The Prevention of Metrazol Fractures by Beta-Erythroidin Hydrochloride, Psychiatric Quart. **14:** 477, 1940.

7. Bennett, A. E.: Preventing Traumatic Complications in Convulsive Shock Therapy by Curare, J. A. M. A. **114:**322-324 (Jan. 27) 1940.

8. Cerletti, U., and Bini, L.: L'elettroshock, Arch. gen. di neurol., psichiat. e psicoanal. **19:**266, 1938.

9. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement: I., J. Biol. Chem. **61:**523-573, 1924.

oxygen saturation of hemoglobin was within normal limits. As a result of the injection of metrazol and erythroidine, the hemoglobin saturation of the arterial blood fell progressively. The lowest oxygen saturation of hemoglobin developed during the postconvulsive phase. After the treatment the oxygen saturation rose rapidly with the resumption of a normal respiratory pattern. Table 2 reveals that the injection of

TABLE 2.—*Effect of Metrazol Convulsions with Curare*

Patient No.	Oxygen Content, Volume per Cent	Oxygen Capacity, Volume per Cent	Hemoglobin Saturation, Percentage	Time Blood Was Drawn in Relation to Convulsions
1	17.70	18.63	95	Before
	12.90	.....	69	During
2	17.50	18.42	95	Before
	16.10	.....	87	Early
	15.10	.....	82	Middle
	7.80	.....	42	Late

TABLE 3.—*Effect of Electrical Shock Convulsions*

Patient No.	Oxygen Content, Volume per Cent	Oxygen Capacity, Volume per Cent	Hemoglobin Saturation, Percentage	Reaction	Time Blood Was Drawn in Relation to Convulsions
1	13.77	14.91	91	Incomplete	Early
	11.61	.....	78	Incomplete	Late
2	3.17	17.60	43	Incomplete	Late
3	6.90	17.10	40	Incomplete	Late
4	2.66	18.63	14	Major seizure	Late
5	9.57	.....	..	Major seizure	Late
	4.44	.....	..	Major seizure	Late
6	10.12	19.94	50	Major seizure	Middle
7	9.06	21.66	42	Major seizure	Late
	1.67	.....	8	Major seizure	Postconvulsive apnea
8	16.75	17.54	91	Major seizure	Early
	11.50	.....	60	Major seizure	Late
9	6.98	19.31	36	Major seizure	Middle
	4.45	.....	23	Major seizure	Late
10	8.48	17.97	41	Major seizure	Late
2	13.11	16.31	80	Major seizure	Early
	10.81	.....	67	Major seizure	Late
7	6.74	21.30	32	Major seizure	Late
	17.41	.....	80	Major seizure	After

metrazol with curare decreases hemoglobin saturation. In table 3 are noted the changes occurring during electrical shock therapy. Most of these patients fell in the depressive and not in the schizophrenic group, but the physiologic changes were the same in the two groups. Here, too, progressive diminution of oxygen saturation is observed during the course of the convulsion. Incomplete convulsions, with only a short tonic phase, are less effective in lowering the oxyhemoglobin saturation of the arterial blood than are the major epileptoid seizures.

The lowest values are obtained in the period of apnea, at the termination of the fit.

COMMENT

It is instructive to contrast the physiologic effects of metrazol convulsions modified by erythroidine or curare with those obtained when metrazol is given without these parasympatheticolytic substances (table 4). It can readily be seen that though the severity of the convulsions is greatly diminished, the unsaturation of hemoglobin may be greater than with metrazol alone. Because of the respiratory paralysis resulting from use of the parasympatheticolytic drugs, the depression

TABLE 4.—*Effect of Metrazol Convulsions on Patients with Schizophrenia*

Patient No.	Oxygen Content, Volume per Cent	Oxygen Capacity, Volume per Cent	Hemoglobin Saturation, Percentage
1	8.70	20.64	42
2	11.17	22.99	49
3	11.43	22.74	50
4	14.05	22.74	62
5	15.35	22.71	68
6	16.45	23.11	71

TABLE 5.—*Effect of Nitrogen Inhalation on Patients with Schizophrenia*

Patient No.	Oxygen Content, Volume per Cent	Oxygen Capacity, Volume per Cent	Hemoglobin Saturation, Percentage
1	2.81	18.32	15
2	3.13	17.37	18
3	3.92	18.03	22
4	4.45	18.57	24
5	4.45	17.91	25
6	5.51	18.17	30

may be profound. The degree of hemoglobin unsaturation is therefore more directly comparable to the results obtained with the nitrogen inhalation therapy (table 5) than to those obtained with the unmodified metrazol treatment. Table 6 reveals the progressive decrease in oxygen saturation which occurs during the inhalation of nitrogen. The decrease of oxygen in the arterial blood with the major epileptoid seizure produced by electrical stimulation is equally marked. Kalinowsky and Horwitz [10] recently reported that the more severe response to electrical shock yields better therapeutic results than does the incomplete reaction. It is possible that the modified forms of metrazol therapy,

10. Kalinowsky, L., and Horwitz, W. A.: The "Petit Mal" Response in Electrical Shock Therapy: Its Theoretical and Therapeutic Significance, read at the ninety-seventh annual meeting of the American Psychiatric Association, Richmond, Va., May 5-9, 1941.

with their more severe depression of the oxygen saturation of the blood, may produce better effects than metrazol given alone.

Loevenhart and co-workers [11] indicated some improvement in schizophrenic patients given injections of sodium cyanide. We, therefore, also determined the effect of cyanide on the brain metabolism of dogs and observed a marked decrease of the cerebral arteriovenous oxygen difference, even greater than that with the insulin treatment [12] (table 7). Recently additional modifications of the shock therapies have appeared. Fabing [13] employed nitrous oxide before the injection of metrazol. In addition to eliminating the apprehension of the patient, the factor of anoxia is intensified by the synergistic action of nitrous oxide and the effect of the convulsive episode in interfering with pulmonary ventila-

TABLE 6.—*Effect of Progressive Anoxia on Hemoglobin Saturation of Patient with Schizophrenia Receiving Nitrogen Inhalation Treatment*

Condition	Oxygen Content, Volume per Cent	Oxygen Capacity, Volume per Cent	Hemoglobin Saturation, Percentage
Loss of contact	4.99	18.24	22
Before termination with oxygen	2.46	18.24	13

TABLE 7.—*Effect of Potassium Cyanide on Cerebral Respiration*

Oxygen, Volume per Cent			Relation of Time Blood Was Drawn to Injection of KCN in Carotid Artery
Arterial	Venous	Difference	
15.93	7.02	8.91	3 min. before
16.92	16.34	0.58	2 min. after 20 mg. of KCN injected
16.37	15.67	0.70	18 min. after injection
15.67	19.96	4.71	1 hr. 32 min. after injection

tion. The effect of nitrous oxide on the hemoglobin saturation of arterial blood is presented in table 8. The average saturation is 83 per cent at the time of loss of contact and 33 per cent during deep surgical anesthesia. In another instance the arteriovenous oxygen difference of the cerebral blood decreased from 5.45 volumes to 0.17 volume per cent during nitrous oxide anesthesia.[14]

11. Loevenhart, A. S.; Lorenz, W. F.; Martin, H. G., and Malone, J. Y.: Stimulation of the Respiration by Sodium Cyanide and Its Clinical Application, Arch. Int. Med. **21**:109-129 (Jan.) 1918. Loevenhart, A. S.; Lorenz, W. F., and Waters, R. M.: Cerebral Stimulation, J. A. M. A. **92**:880-883 (March 16) 1929.

12. Fazekas, J. F.; Colyer, H., and Himwich, H. E.: Effect of Cyanide on Cerebral Metabolism, Proc. Soc. Exper. Biol. & Med. **42**:496-498, 1939.

13. Fabing, H. D.: Induction of Metrazol Convulsions with the Patient Under Nitrous Oxide Anesthesia, Arch. Neurol. & Psychiat. **47**:223-233 (Feb.) 1942.

14. Himwich, H. E.; Martin, S. J.; Alexander, F. A. D., and Fazekas, J. F.: Electrocardiographic Changes During Hypoglycemia and Anoxemia, Endocrinology **24**:536-541, 1939.

The results show that deficient pulmonary ventilation is associated with shock therapies other than the insulin method. Magnesium sulfate has also been used to diminish the severity of the convulsion produced by the injection of metrazol.[15] It may be anticipated that with this drug, too, some degree of anoxemia is developed. On the other hand, cyanide inhibits cerebral cellular respiration by inactivating cytochrome oxidase. From a comparison of these various methods with insulin hypoglycemia, it may be said that though the final degree of cerebral depression may be as deep in all instances, that of hypoglycemia persists for a longer period, up to two or three hours. With nitrogen inhalation the duration of hypoxia and that of the succeeding anoxia are approximately two minutes each. With the shock therapies they are shorter, from one to two minutes.

The relation between the cerebral depression and the amelioration of schizophrenia is still undetermined. Records of electrical brain

TABLE 8.—*Effect of Nitrous Oxide Anesthesia on Arterial Oxygen Relations*

	Loss of Contact			Surgical Anesthesia		
Patient	Content, Volume per Cent	Capacity, Volume ped Cent	Hemoglobin Saturation, Percentage	Content, Volume per Cent	Capacity, Volume per Cent	Hemoglobin Saturation, Percentage
1	17.59	20.41	86	4.44	21.50	21
2	16.92	18.52	91	7.35	19.88	37
3	15.32	16.26	99	4.44	16.11	28
4	12.68	20.41	62	9.00	20.61	44
Average			83			33

potentials made after anoxia indicate a transition period of hyperactivity before the electroencephalogram returns to normal. Gerard[16] suggested that this short period of cerebral hyperactivity which precedes the return to normal may be the cause of the amelioration in the clinical picture. However, it has not been possible to demonstrate augmented brain metabolism following insulin hypoglycemia. Though the methods are relatively crude, the arteriovenous oxygen difference is not increased[17] and the blood flow is not altered significantly.[2] The admin-

15. Yaskin, H. E.: Prevention of Traumatic Complications in Convulsive Shock Therapy by Magnesium Sulfate, Arch. Neurol. & Psychiat. **46**:81-85 (July) 1941.

16. Gerard, R. W.: Anoxia and Neural Metabolism, Arch. Neurol. & Psychiat. **40**:985-996 (Nov.) 1938.

17. Himwich, H. E.; Hadidian, Z.; Fazekas, J. F., and Hoagland, H.: Cerebral Metabolism and Electrical Activity During Insulin Hypoglycemia in Man, Am. J. Physiol. **125**:578-585, 1939. Loman, J.: Sugar and Oxygen Metabolism of the Brain During and After Insulin Hypoglycemia, Arch. Neurol. & Psychiat. **45**:282-288 (Feb.) 1941. Wortis, J.; Bowman, K. M., and Goldfarb, W.: Human Brain Metabolism, Normal Values and Values in Certain Clinical States, Am. J. Psychiat. **97**:552-565, 1940.

istration of such stimulants as thyroid,[18] pyocyanine [19] and methylthionine chloride (methylene blue) [20] have not influenced the course of schizophrenia.

Another physiologic explanation is concerned with sluggish reactivity of the sympathetic [21] division of the autonomic nervous system in patients with schizophrenia. According to Gellhorn,[22] these treatments produce an ameliorative effect by increasing the activity of this branch of the autonomic nervous system. But this hyperactivity is a temporary phenomenon. Moreover, the administration of epinephrine [23] or the sympatheticomimetic drugs ephedrine and amphetamine (benzedrine) [24] fails to produce the effects on the clinical picture of schizophrenia similar to those of the shock therapies. This applies as well to the parasympatheticomimetic drugs [25] acetylcholine, compounds of acetylcholine and physostigmine. Atropine is also ineffective.[26]

Perhaps the most striking clinical change during the treatment is the development of symptoms indicating depression of the activity of the higher cerebral centers and release of the lower. Later these, too, become depressed. Not only are the results of these physiologic alterations apparent in the psychotic outbursts toward the end of the first stage, but the symptom complex of each succeeding stage is a manifestation of the same phenomenon. This release is recapitulated at each functional level as the processes of recovery ascend the neuraxis and before the patient undergoes a second psychotic episode. It may be

18. Hoskins, R. G., and Sleeper, F. H.: The Thyroid Factor in Dementia Praecox, Am. J. Psychiat. **10**:411-432, 1930.

19. Tietz, E. B.: Personal communication to the authors.

20. Gildea, E. F.; Himwich, H. E.; Hubbard, O. E., and Fazekas, J. F.: A Comparative Study of Some of the Changes Produced by Various Types of Drugs in Schizophrenic Patients, Am. J. Psychiat. **91**:1289-1309, 1935.

21. Hoskins, R. G., and Jellinek, E. M.: The Schizophrenic Personality with Special Regard to Psychologic and Organic Concomitants, A. Research Nerv. & Ment. Dis., Proc. **14**:211-233, 1933.

22. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **40**:125-146 (July) 1938.

23. Dynes, J. B., and Tod, H.: The Emotional and Somatic Response of Schizophrenic Patients and Normal Controls to Adrenalin and Doryl, J. Neurol. & Psychiat. **3**:1-8, 1940.

24. (*a*) Myerson, A.: The Effects of the Sympatheticomimetic Drug Benzedrine on the Viscera and the Mood of Man, Psychol. Bull. **33**:746, 1936. (*b*) Cameron, D. E.: Objective and Experimental Psychiatry, ed. 2, New York, The Macmillan Company, 1941, pp. 271-272.

25. Dynes and Tod.[23] Cameron.[24b]

26. Myerson, A.: Human Autonomic Pharmacology: XII. Theories and Results of Autonomic Drug Administration, J. A. M. A. **110**:101-103 (Jan. 8) 1938.

that depression of brain metabolism, with the eclipse of cortical functions, facilitates the change in behavior by permitting an expression of the more primitive cerebral mechanisms mediated by the subcortex but ordinarily held in cortical control. From this point of view the shock therapies may be regarded as excellent examples of Hughlings Jackson's conception of the evolution and dissolution of the nervous system,[27] with the temporary dissolution resulting from the treatments as a therapeutic mechanism.

Depression of brain metabolism carried to a further stage leaves the physiologic field and enters the pathologic; destruction of brain cells occurs. Such changes in the brain may alter the patient's behavior. The damage may be of a scattered histologic nature, usually leaving no residual neurologic symptoms.[28] When hypoxia or hypoglycemia is too prolonged, widespread degeneration of the brain may ensue.

In the convulsion therapies the phenomena of hypoxia are complicated by the effects produced by electrical stimulation or by metrazol or any of the other drugs that are used. The therapeutic significance of hypoxia per se can be determined only by a study of its effects uncomplicated by other factors. For this reason, an investigation of the therapeutic results of nitrogen inhalation is now in progress at the Brooklyn State Hospital.

SUMMARY AND CONCLUSIONS

Patients with schizophrenia receiving various forms of shock therapy were studied. It was found that the oxygen saturation of the arterial blood diminished with the metrazol treatment when the convulsions were modified by administration of erythroidine or curare. Electrical shock therapy also revealed depression of the oxygen supply to the brain. A comparison was made between these physiologic results and those obtained with other therapeutic agents: (*a*) metrazol alone, (*b*) potassium cyanide and (*c*) insulin. With all these hypoxia occurred, with consequent depression of brain metabolism. The relation of this depression to the ameliorative effect on the course of the disease is discussed.

Drs. D. E. Cameron, M. V. Borenstein and J. D. Sullivan, of the Albany Hospital, and Drs. K. M. Bowman and W. Goldfarb, of the Bellevue Psychiatric Hospital, cooperated with us in obtaining these observations.

27. Jackson, J. H.: The Croonian Lectures on Evolution and Dissolution of the Nervous System, Brit. M. J. **1**:591, 660 and 703, 1884.

28. Tannenberg, J.: Advantages and Danger of Combined Anoxic and Insulin Shock, Arch. Neurol. & Psychiat. **44**:811-828 (Oct.) 1940.

PARAPYRAMIDAL FASCICULOTOMY IN THE BRAIN STEM

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The surgical interruption of the parapyramidal pathways at the cervical level in cases of adventitious movement due to disease of the basal ganglia has not been uniformly successful, partly, it is thought, because the level of section has not been sufficiently high to interrupt the more cephalic neuromuscular innervations. To test this hypothesis it was decided to make an effort to secure interruption of the parapyramidal complex at a point in the brain stem where it might be

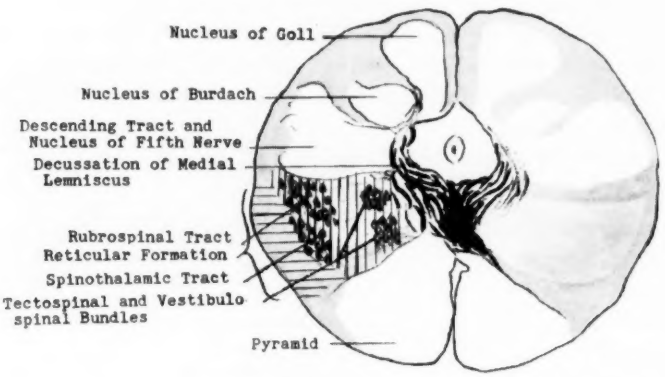

Fig. 1.—Cross section of the medulla at the level of the decussation of the medial lemniscus, illustrating the region of the projected incision.

reasonably superficial. It was felt that section of the rubrospinal tract cephalad to the pyramidal decussation would offer less chance of coincident injury to the corticospinal pathway. The actual course of the various parapyramidal pathways in the human brain stem is as yet imperfectly understood. Opinion, however, tends to favor the reticular formation in the medulla as including the rubrospinal, tectospinal and vestibulospinal bundles. The first of these occupies a position between the descending trigeminal and the spinothalamic tracts. The last two have a more medial situation (fig. 1). At a point just caudal to the inferior olive the reticular formation is fairly superficial and surgically approachable. Accordingly, the region was subjected to

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careful anatomic scrutiny, and after certain technical considerations had been taken into account, a plan of operative procedure was worked out.

ANATOMIC AND TECHNICAL CONSIDERATIONS

The reticular formation is most superficial at the level of the decussation of the medial lemniscus, just cephalad to the pyramidal decussation. In addition to the various parapyramidal bundles mentioned, the spinothalamic tract is situated in this region, between the pyramid anteriorly and the tuberculum cinereum posteriorly. The surface of the brain stem covering the reticular formation at this level

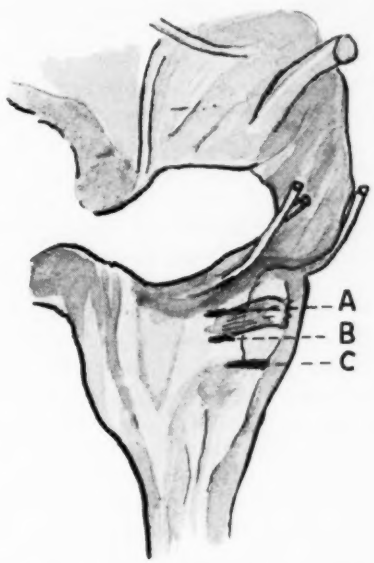

Fig. 2.—Lateral surface of the brain stem, illustrating sites for descending trigeminal, spinothalamic and parapyramidal fasciculotomy—*A*, *B* and *C*, respectively.

is overlaid by the vertebral artery, just cephalad to the point at which the posterior inferior cerebellar artery is given off. Other landmarks are the twelfth cranial and the first cervical nerves, lying anteriorly, the eleventh cranial nerve, lying posteriorly, and the obex, the level of which is practically the same as that of the projected incision. The accessibility of the eleventh cranial and first cervical nerves makes possible the section of these structures when torticollis coexists.

The procedure of fasciculotomy in the human brain stem has been carried out previously for other conditions. It was introduced by

Sjöqvist,[1] who sectioned the descending tract of the fifth cranial nerve to secure relief from pain in trigeminal neuralgia. More recently Schwartz and O'Leary [2] reported on section of the spinothalamic tract at the medullary level. The incision of Sjöqvist is more cephalic and dorsal than that utilized for projected parapyramidal fasciculotomy. The section of Schwartz and O'Leary is also more cephalic and dorsal, though not made as far cephalad as the Sjöqvist incision. Figure 2 illustrates the relative sites of the three incisions.

The interest inherent in the following case stems from the fact that it represents an effort to interrupt the parapyramidal fiber tracts at a level more cephalic than that of the usual chordotomy and, because of the necessary coincidental section of the nearby spinothalamic pathway, serves to add to the growing body of data concerning the medullary representation of pain and temperature sensibility.

REPORT OF A CASE

A woman aged 38. Postencephalitic parkinsonism involving tremor and rigidity of all limbs, particularly the right upper extremity. Right parapyramidal fasciculotomy in brain stem at level of inferior olive. Marked diminution of tremor promptly following operation, with gradual reappearance. Neurologic status at time of discharge unaltered, except for hypalgesia and hypothermesthesia from third lumbar through fifth sacral dermatome on left. Touch, vibration and muscle-joint sensibility preserved. Trigeminal sensation undisturbed.

History.—M. D., a 38 year old white woman, was admitted to the Jewish Hospital of Brooklyn on June 19, 1941. She complained chiefly of tremor and rigidity of the right limbs. She had had "influenza" in 1918, at the onset of which she was unconscious for three days and subsequently was bedridden for six months. She apparently was without notable sequelae until 1929, when tremor first appeared in the right limbs. Subsequently similar involvement developed in the left extremities, and more recently tremor of the head appeared. The patient had become increasingly irritable and emotionally labile during the year prior to admission. She had received various forms of medicinal therapy, including scopolamine. This drug when administered in large amounts effected slight diminution of the tremor.

Of interest in the past history was a right nephrectomy for a tuberculous kidney in 1933. The family history was not significant with respect to the patient's illness.

Examination.—No disturbance of memory, orientation, central speech function, nonequilibratory coordination, sensation or motor power was noted. The significant neurologic findings included a festinating gait, loss of associated movements, masking of the facies, monotonous, mumbling speech, fixation of pupils to light, weakness of the left internal rectus muscle and divergent strabismus. There was generalized hypertonus of slight degree. A fine rhythmic tremor was present in all the limbs, being most marked in the right upper extremity. Its frequency was about 200

1. Sjöqvist, O.: The Conduction of Pain in the Fifth Nerve and Its Bearing on the Treatment of Trigeminal Neuralgia, Yale J. Biol. & Med. **2**:593-600 (July) 1939.

2. Schwartz, H. G., and O'Leary, J. L.: Section of the Spinothalamic Tract in the Medulla with Observations on the Pathway for Pain, Surgery **9**:183-193 (Feb.) 1941.

per minute and its maximum amplitude about 10 cm. The tremor tended to cease with voluntary motor activity, such as holding the hands outstretched or performing the heel to knee test.

Laboratory Data.—The blood count, serologic tests, chemical studies of the blood and urinalysis showed nothing of particular significance. The cerebrospinal fluid was under a pressure of 158 mm. of water and contained 2 lymphocytes per cubic millimeter. The Wassermann and colloidal gold reactions of the fluid were negative. Roentgenograms of the chest and skull revealed no abnormalities.

Operation.—A right suboccipital hemicraniectomy was carried out with the patient under general anesthesia. The horseshoe-shaped musculocutaneous flap was carried slightly across the midline to permit adequate exposure of the brain stem and cerebellar tonsils. This was also facilitated by removal of the arch of the atlas. After reflecting a dural flap, with its pedicle toward the midline, the right cerebellar tonsil was retracted to expose that portion of the medulla anterior to the tuberculum cinereum. To do this adequately it was necessary to retract the vertebral artery laterally and to sever a vessel situated somewhat caudal to the projected incision, running from the spinal accessory nerve to the medulla. Due exposure having been made, the medulla was incised to a depth of 4 mm., beginning anterior to the rootlets of the spinal accessory nerve and carrying the incision dorsally a distance of 4 mm., thereby reaching the tuberculum cinereum. The incision corresponded roughly to the inferior extremity of the olive, slightly caudal to the obex. The wound was closed in layers with interrupted black silk sutures.

Subsequent Course.—During the first three weeks following operation the patient's tremor was greatly diminished, at times disappearing completely. This status was evident promptly after operation. On the fifth postoperative day an unexplained fever developed, and the patient became progressively more lethargic, so that tube feeding became necessary. The condition, in fact, suggested an acute exacerbation of chronic encephalitis. After two weeks the fever subsided and she became increasingly alert. The tremor, however, slowly reappeared and by the time of the patient's discharge had attained its former intensity. The neurologic status was unaltered, except for the presence of hypalgesia and hypothermesthesia from the third lumbar through the fifth sacral dermatome on the left. Touch, vibration and muscle-joint sensibility were preserved. Trigeminal sensation was undisturbed.

COMMENT

This report represents necessarily only a preliminary study of the feasibility of interrupting the parapyramidal pathways within the brain stem for the purpose of securing relief from adventitious movement secondary to disease of the basal ganglia. Without necropsy material and stained preparations for degenerated fiber tracts, it is impossible to state whether these particular pathways were actually sectioned and whether interruption of cephalic innervations not possible in chordotomy is feasible. From the results in this particular case one can only infer that such action was effected, the inference being based on the concomitant impairment of pain and temperature sensation contralaterally and the assumption that the spinothalamic and extrapyramidal pathways are situated in and near the reticular formation and were therefore included in the incision. However, the fact that the tremor practically disappeared for about two weeks after operation despite the retention of

motor power suggests that such interruption was only physiologic and was attributable to edema contiguous to the incision. This view is supported by the fact that the descending trigeminal fibers escaped involvement. Actual section of the rubrospinal pathway without some implication of the two fiber bundles between which it lies appears improbable. Their concomitant involvement, on the other hand, would offer reasonably good clinical evidence that the rubrospinal fibers had been interrupted.

The completion of this study will have to await the examination of Marchi preparations as these become available with necropsy material. Such an opportunity may arise as the operation of high spinothalamic fasciculotomy introduced by Schwartz finds wider application. White [3] has had occasion to utilize this operation, with satisfactory results.

The experience of Putnam [4] with extrapyramidal chordotomy suggests that tremor and rigidity are not as favorably influenced as athetosis. A continued investigation of the possibilities of section at higher levels should therefore include cases of the latter type.

Of incidental interest in this study is the light thrown on the question of the segmental representation of pain and temperature sensibility at the inferior olivary level. The escape of the more cephalic dermatomes suggests that they are more medially represented within the reticular formation than those fibers coming from the caudal segments and tends to confirm the observation of Walker [5] regarding the topical arrangement of spinothalamic fibers in the medulla.

SUMMARY

Reported herein is the study of a case of postencephalitic parkinsonism in which an incision into the region of the reticular formation in the medulla was made in the hope of interrupting parapyramidal pathways at a level more cephalic than is obtained by chordotomy. Relief was only transitory. Impairment of pain and temperature sensation in the contralateral lower limb was secured. Trigeminal sensation was undisturbed.

The possibilities for further investigation of this problem are discussed.

The significance of the resultant sensory loss is considered.

80 Hanson Place.

3. White, J. C.: Spinothalamic Tractotomy in the Medulla Oblongata: An Operation in the Relief of Intractable Neuralgias of the Occiput, Neck and Shoulder, Arch. Surg. **43**:113-127 (July) 1941.

4. Putnam, T. J.: Results of Treatment of Athetosis by Section of the Extrapyramidal Tracts in the Spinal Cord, Arch. Neurol. & Psychiat. **39**:258-275 (Feb.) 1938.

5. Walker, A. E.: The Spinothalamic Tract in Man, Arch. Neurol. & Psychiat. **43**:284-298 (Feb.) 1940.

STUDIES OF THE SENSATION OF VIBRATION

II. VIBRATION SENSIBILITY IN THE FACE FOLLOWING RETROGASSERIAN NEURECTOMY

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At present there are four different theories as to the mechanism by which vibratory stimuli are perceived. Early clinical studies made with the vibrating tuning fork as the source of stimulation convinced many investigators that vibration sensibility was nothing more than the perception of repetitive mechanical stimuli delivered to the so-called deep receptors. Among these are included the pressure receptors of the skin and subcutaneous tissues, which are stimulated by mechanical forces that deform the surface of the skin, as well as those sense organs which respond to mechanical stimulation and lie in the fascia, muscles, tendons, joint capsules and periosteum of bones. Later, under the stimulus of work by von Frey,[1] the opinion arose that vibration was perceived by means of repetitive mechanical stimulation to the tactile receptors located in the skin and not by any other sense organs. Von Frey expressed the belief that the bone to which a tuning fork is applied during clinical examination was merely an insensitive resonator for the transmission of vibrations to tactile end organs. In 1930 Katz[2] concluded that vibration was perceived neither by the deep pressure receptors nor by the superficial tactile sense organs but instead by means of an independent group of sense organs the sole function of which is to subserve the vibration sense. The innervation and location of these sense organs were not described by him. The fourth explanation of vibratory sensibility was first suggested by Allen and Hollenberg.[3] They studied the fusion threshold for repetitive stimulation by directing pulsations of air against the intact skin. Because they found two distinct thresholds of fusion

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1. von Frey, M.: Die Vergleichung von Gewichten mit Hilfe des Kraftsinns, Ztschr. f. Biol. **65**:203, 1915.

2. Katz, D.: The Vibratory Sense and Other Lectures, Bulletin 32, no. 10, Orono, Maine, University of Maine, 1930.

3. Allen, F., and Hollenberg, A.: On the Tactile Sensory Reflex, Quart. J. Exper. Physiol. **14**:351, 1924.

they concluded that one threshold represented the fusion point for the pressure receptors and the other the fusion point for the tactile end organs. This, in turn, suggests that vibrating objects may stimulate either or both types of sense organs to produce the sensation of vibration. Pollock,[4] in 1937, adduced additional evidence which supported this last view. He showed that an area of skin deprived of epicritic and protopathic sensibility could still mediate vibratory stimuli and that the vibration sensibility left in such skin was of a different order from that perceived in normal skin.

In this communication additional evidence is presented to show that the reception of vibratory stimuli occurs by means of the deep pressure sense organs as well as by the superficial tactile receptors. Like Pollock, we studied patients who had been subjected to retrogasserian neurectomy for the relief of trigeminal neuralgia. As is well known, the face loses all touch, pain and temperature sensibility after this procedure, whereas pressure and pressure-pain sensibility remains intact. One may reasonably anticipate that vibration sensibility would suffer no impairment in the face after resection of the trigeminal nerve root if the vibratory stimuli are mediated exclusively through pressure receptors. On the other hand, if the tactile end organs are the sole source of this sensory modality, total loss of vibratory sensations in the face should follow retrogasserian neurectomy. Either total loss or total preservation of vibration sensibility should follow this operation if the view of Katz is correct, for it is unlikely that a group of sensory endings devoted exclusively to the reception of vibratory stimuli would receive innervation from both the deep nerve fibers of the facial nerve and those of the trigeminal nerve. Finally, if the view that both deep pressure receptors and tactile end organs are capable of mediating vibratory stimuli is correct, it is to be expected that our subjects would lose a portion, but not all, of the vibration sensibility in the face after trigeminal resection.

MATERIAL AND METHODS

Quantitative threshold studies of vibration sensibility in the face were made on 9 patients who had been subjected to unilateral retrogasserian neurectomy by Dr. Loyal Davis from one month to eleven years prior to the present investigation. Five of the subjects were men and 4 women; their ages ranged from 48 to 80 years. In all subjects complete loss of touch, pain and temperature sensibility was demonstrated in the entire area supplied by the trigeminal nerve. Pressure sufficient to produce visible deformation of the skin was instantly perceived and accurately localized by all subjects in the areas examined for vibration sensitivity. Little or no loss of motor power was present in the muscles supplied by the motor division of the trigeminal nerve.

4. Pollock, L. J.: Vibration Sense, Arch. Neurol. & Psychiat. **37**:1383 (June) 1937.

The instrument used as a source of vibratory stimuli was constructed so as to avoid a number of errors which have been introduced into the literature by the use of less precise apparatus. It is capable of delivering from 100 to 3,000 double vibrations per second of true sinusoidal character, so that stimulation by harmonics, or secondarily produced oscillations, was avoided within the limits of the instrument. The behavior of the stimulating point while in actual use against the skin was considered the stimulus, and not its behavior postulated from knowledge of the energy delivered to the point before it is put in use. In this way we believe that the character of the oscillations, as well as their frequency and amplitude, was determined as they were actually delivered to the skin. The effect of dampening by the skin could easily be appraised and held in check. Accordingly, the apparatus used in the present investigation consists of two units, a driving and a recording unit. The unit for driving the stimulating point includes a vacuum tube oscillator, a three stage radio amplifier and an electrodynamic speaker to which the vibrating point is attached (fig. 1). This consists of a pointed cylindric piece of aluminum. The recording unit comprises a rochelle salt crystal which is

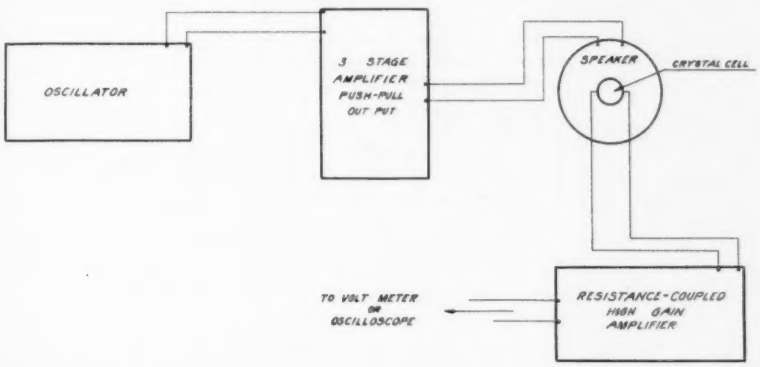

Fig. 1.—Diagram of the apparatus for the study of mechanical vibration. Oscillator: Clough-Brengle beat frequency; three stage amplifier: resistance-coupled, push-pull parallel output, A. C.–operated; speaker (Jensen): permanent magnet, pot voice coil and spider; crystal: brush inertia type piezoelectric vibration pick-up; amplifier: battery-operated, dual input, three stage resistance-coupled, connected to another amplifier with the same characteristics as the one described above.

housed within a cell mounted directly on the stimulating point, so that movements of the point are at all times producing an electrical change in the crystal (fig. 2). The oscillating current so produced is analyzed by means of a high gain amplifier, a cathode ray oscilloscope and appropriate voltmeters. By suitable calibrations described elsewhere [5] the character of the vibrations, their frequency and amplitude could be accurately determined for the stimulating points while in actual use.

Five points on each side of the face were studied in each subject. The first of these was in the frontal area about 1 cm. above the midpoint of the eyebrow.

5. Yacorzynski, G. K., and Brown, M.: Studies of the Sensation of Vibration: I. Variability of the Vibratory Threshold as a Function of Amplitude and Frequency of Mechanical Vibration, J. Exper. Psychol. **28**:509, 1941.

The second point was over the approximate center of the fat pad in the cheek. The third and the fourth point were located in the upper and the lower lip, respectively, about 1 cm. above and below the vermilion border at a point midway between the center of the lip and the lateral angle of the mouth. A spot on the tongue at the angle made by its distal and lateral edges constituted the fifth point. None of the points tested was the seat of indurative or trophic disturbances.

During the examination the patient was seated in a chair alongside the vibrating point. His head was moved toward the point by the examiner until contact was just established. An effort was made to avoid deep pressure on the face by the vibrating point.

The procedure used for the measurement of thresholds to vibrating stimuli was a modification of the constant psychophysical method. The threshold amplitudes were all determined for vibrations of 100 double vibrations per second. To obtain this threshold the apparatus was set in motion either at a greater or at a lesser amplitude than the subject's threshold (as determined by preliminary testing). The amplitude was then brought in the direction of the threshold (by reducing or increasing it) in small steps. At each amplitude setting the face of the subject

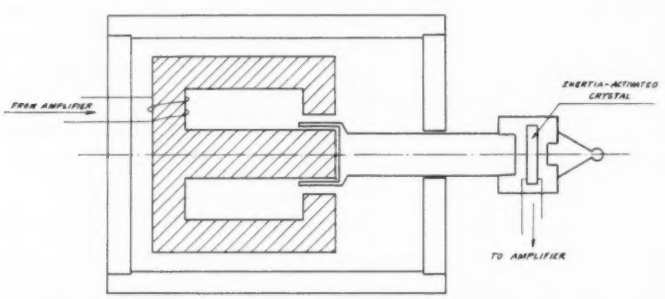

Fig. 2.—Diagram of the attachment of the aluminum housing, containing the rochelle salt crystals, on the core (stimulator) of the electrodynamic speaker.

TABLE 1.—*Maximum Amplitude Delivered by the Apparatus at Frequencies from 100 to 1000 Double Vibrations*

Frequency, d. v.	100	200	300	400	500	600	700	800	900	1,000
Amplitude, 10^{-4} cm.	458	92	38	21	15	9	7	5	4	3

was brought to the vibrating point until he reported that the vibration was lost or had just been perceived. Four threshold determinations were made for each point tested in both a descending and an ascending order of stimulation. In a previous communication we showed that this procedure will give a statistically reliable threshold value. In addition, the maximum frequency of vibration which could be felt at each point was ascertained; the amplitudes used at these critical frequencies were the maximum which could be delivered by the apparatus used. In table 1 may be seen the maximum amplitudes of vibrations which could be delivered by our apparatus in the range of frequencies (100 to 1000 double vibrations) which were used in this study.

RESULTS OF INVESTIGATION

In table 2 may be seen the thresholds for the amplitude of vibrations perceived at a frequency of 100 double vibrations per second for the 9 subjects. Examination of this table shows interesting differences

TABLE 2.—*Thresholds of Vibration Sensibility in the Face After Retrogasserian Neurectomy to Stimuli of a Frequency of 100 Double Vibrations per Second* *

Subject	1	2	3	4	5	6	7	8	9
Point 1									
Normal side	180	41	5	11	198	22	31	44	209
Anesthetic side	None	225	None	None	None	None	None	None	None
Point 2									
Normal side	83	155	18	31	198	24	42	359	14
Anesthetic side	None	None	None	None	283	None	None	None	None
Point 3									
Normal side	12	9	12	..	7	15	7	221	8
Anesthetic side	118	38	37	..	86	22	54	None	44
Point 4									
Normal side	50	8	12	12	..	18	8	128	15
Anesthetic side	None	59	38	None	..	142	26	None	44
Point 5									
Normal side	7	8	3	10	..	9	9	77	12
Anesthetic side	186	144	288	116	..	353	57	255	43

* Amplitudes of thresholds are expressed as centimeters $\times 10^{-4}$.

TABLE 3.—*Maximum Frequency of Vibration Perceived in the Face after Retrogasserian Neurectomy* *

Subject	1	2	3	4	5	6	7	8	9
Point 1									
Normal side	200	200	1,000	700	250	450	500	250	500
Anesthetic side	None	150	None	None	None	None	None	None	None
Point 2									
Normal side	250	250	700	...	250	450	350	250	500
Anesthetic side	None	None	None	None	200	None	None	None	None
Point 3									
Normal side	400	500	500	...	500	400	400	200	700
Anesthetic side	100	150	100	...	...	100	100	None	150
Point 4									
Normal side	200	600	700	400	...	400	400	150	600
Anesthetic side	None	150	100	None	...	100	100	None	150
Point 5									
Normal side	600	650	900	...	...	750	600	300	750
Anesthetic side	500	450	450	...	...	150	250	150	150

* The upper limit is expressed as the number of double vibrations per second.

between the two sides of the face. At a frequency of 100 double vibrations per second vibration sensibility was lost at points 1 and 2 in the face on the side of operation, with but 2 exceptions. In subjects 2 and 5 there was not a loss of but a decided increase in vibration sensibility in these 2 cases. However, vibrations delivered by our equipment at 100 double vibrations per second failed to be perceived only once at point 3

and three times at point 4. In all other trials vibratory sensibility persisted at points 3, 4 and 5, but the threshold was considerably increased as compared with that on the intact side of the face. It appears that the deprivation of tactile sensibility in the face causes a loss of vibration sensibility in some parts and a diminution in others within the limits of stimulation imposed by our apparatus. The upper limit of frequency of vibration which can be perceived when the amplitude of vibration is the greatest that can be delivered by the equipment is shown in table 3. Here, too, one may see that areas 1 and 2 on the anesthetic side cannot transmit vibratory sensations at any frequency, with the exception of 2 instances, in which the rate of fusion was distinctly lower than that of the normal side of the face. In 18 of 22 instances vibration sensibility was preserved in the lips and tongue after trigeminal neurectomy, and in all these cases the maximum frequency of vibration which could be perceived was considerably lower than the maximum for the normal side of the lips and tongue. In 4 instances no vibrations could be felt in these areas also. Summing up the observations, as shown in tables 2 and 3, it appears that the skin of the forehead and cheek is capable of receiving little or no mechanical vibration after it has been deprived of tactile sensibility, whereas the skin of the lips and the tongue under the same conditions suffers diminution, but not total loss, of vibration sensibility.

COMMENT

Examination of the foregoing data immediately raises the question why the forehead and cheek should differ from the lips and tongue in their response to vibration after section of the trigeminal root. An explanation that suggests itself is the fact that the lips and tongue contain considerably more muscle fibers than does the skin of the forehead and cheek. Correlated with this greater occurrence of muscular tissue there is probably a greater number of deep pressure sense organs. The vibrating point, it should be remembered, was presented to the skin with no more pressure than was required to establish mere contact between the skin and the vibrating point, so that pressure receptors were stimulated to a minimum. To confirm this is the fact that patients who failed to feel the vibration when the vibrating point was touched to the forehead also failed to perceive its contact and hence did not know they were being stimulated. In the lips, however, the lightest contact with the vibrating point was immediately perceived, as also were vibrations of proper amplitude and frequency. In several subjects we could show that by increasing the pressure exerted by the vibrating point, that is, by producing a greater deformation of the skin surface, the vibration sensibility was considerably enhanced but still fell far short of the corresponding area on the normal side. In several instances deep pressure with the

vibrating point over the skin of the forehead resulted in the appearance of vibration sensibility which was absent with the usual mode of stimulation. This suggests that sensations of vibration are mediated by pressure receptors if the vibrating object delivers enough energy to these sense organs.

The question of spread of vibration from insensitive areas of skin to sensitive areas also must be considered at this point. With the apparatus used in the present study we believe this factor plays an insignificant role. First, vibrations perceived in the anesthetic half of the face were always sharply localized to the actual point of stimulation. Second, the forehead, which one might expect to act as a good resonator for the spread of vibrations to the normal side, was least sensitive after trigeminal root section. A piezoelectric crystal placed on the skin alongside the area stimulated showed little transmitted vibration to the normal side. We could also demonstrate that effective blocking of vibratory spread to the normal side when the anesthetic side was being stimulated did not cause any significant increase in the threshold. The blocking of vibratory spread was produced by pressure on the skin in the midline of the face and was shown to be effective by the absence of any vibration in the piezoelectric crystal pick-up from the nonstimulated side of the face.

The vibration sensibility of the tongue deserves considerable interest. Many writers state that the tongue is insensitive to vibration. It is insensitive if the base of a vibrating tuning fork is applied to its surface, but it is far from so when the prongs of that fork are used as a stimulus. With our apparatus the tongue was found to be exquisitely sensitive to vibrations, as reference to tables 2 and 3 will promptly show. On the anesthetic side of the tongue there was a reduction in the acuity of vibration sensibility but never a loss. Associated with this reduction was an interesting subjective change in the character of the vibration. A sense of tickle was present on the normal side of the tongue when it was stimulated by the vibratory point, but it was absent in some cases on the anesthetic side of the tongue, despite the presence of vibration sensibility. In other words, section of the trigeminal root caused not only a quantitative change in vibration sensibility of the tongue but a qualitative change in some cases.

SUMMARY AND CONCLUSIONS

Vibration sensibility was studied in the faces of 9 patients who had been subjected to unilateral retrogasserian neurectomy. Thresholds of vibration sensibility at frequencies of 100 double vibrations per second were ascertained for five different points on each side of the face and tongue, and the upper limit of frequency of vibration perceived was determined at these points under the limitation imposed by our apparatus.

We found that the loss of tactile sensibility and the preservation of pressure sensibility in the face are associated with diminution in vibratory sensibility in the lips and tongue. On the forehead and cheek vibration delivered by our apparatus under the conditions of the present experiment could not be perceived in most instances. It is suggested that the perception of vibratory stimuli in the face depends on the stimulation of both touch and deep pressure receptors. Vibration sensibility therefore is to be regarded as the perception of repetitive mechanical stimuli delivered either to deep or to superficial receptors or to both varieties. The type of apparatus used, the manner in which it is used and the innervation of areas stimulated determine the relative importance of pressure on tactile end organs in the perception of vibration.

Dr. Lewis J. Pollock and Dr. Loyal Davis made available to us the patients used in this study.

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ELECTROENCEPHALOGRAMS OF THIAMINE-DEFICIENT PIGEONS

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In acutely thiamine-deficient pigeons marked impairment of function of the central nervous system develops, associated with a characteristic and progressive series of head and neck movements and degeneration of certain neurons (Swank [1]; Swank and Bessey [2]; Swank and Prados [3]). The first of these movements consists of rhythmic lateral rotation of the head alone or combined with extensor thrusts of the neck and has been designated preopisthotonos. This phase may last from a few to twenty-four hours and in progressive thiamine deficiency is followed by complete opisthotonos. If the deficiency is allowed to become more severe, and death does not intervene, opisthotonos is followed by slow relaxation; the pigeon can no longer elevate its head above the horizontal and is generally listless. This final stage, enopisthotonos, is followed by death within a few hours if thiamine is not administered.

Histologic studies (Swank [1]; Swank and Prados [3]) have revealed progressive neuronal degeneration, which appeared first in the vestibular proprioceptive system during preopisthotonos. When opisthotonos had been present for some time, especially during enopisthotonos, degeneration in this system became much more severe and was to be observed also in the cerebellum, the optic system and, to a less extent, throughout the brain. Since the clinical manifestations quickly disappeared under treatment with thiamine, one must assume that functional impairment had occurred in many neurons which did not appear in histologic sections to be degenerating. It seems reasonable to assume, however, that

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1. Swank, R. L.: Avian Thiamin Deficiency: A Correlation of the Pathology and Clinical Behavior, J. Exper. Med. **71**:683, 1940.

2. Swank, R. L., and Bessey, O. A.: Avian Thiamin Deficiency: III. Characteristic Symptoms and Their Pathogenesis, J. Nutrition **22**:77, 1941.

3. Swank, R. L., and Prados, M.: Avian Thiamin Deficiency: II. Pathological Changes in the Brain and Cranial Nerves (Especially the Vestibular) and Their Relationship to the Clinical Behavior, Arch. Neurol. & Psychiat. **47**:97 (Jan.) 1942.

histologic degeneration is an index of the degree to which neighboring neurons are impaired functionally.

Changes in the electrical activity of the brain would be expected to occur at least during the more advanced stages of disturbed function and structure, especially since carbohydrate metabolism is so impaired by thiamine deficiency. Tokaji and Gerard [4] observed certain complex changes in the brain potentials of pigeons subjected to a diet deficient in vitamine B_1. Their birds consumed the diet ad libitum; therefore it must be assumed that starvation was also present, since starvation always accompanies thiamine deficiency under these circumstances.[1] No attempt was made to correlate the changes in brain potentials with the functional and histologic signs of damage to nerve cells.

The purpose of this study was to attempt such a correlation and to clarify the effect of thiamine deficiency (alone) on the electroencephalogram.

METHOD AND MATERIAL

Several species of pigeons, all obtained in the vicinity of Montreal, were used in this study. They (30 in all) were made deficient in thiamine by tube feeding 15 to 20 Gm. of a purified ration consisting of casein (20 per cent), cod liver oil (4 per cent), peanut oil (5 per cent), salt mixture (2 per cent), corn starch (59 per cent), autoclaved bakers' yeast (10 per cent) and an excess of vitamin K. Two or three control electroencephalograms were taken before the diet was begun, and subsequent records were taken on the first, fourth and seventh days of the regimen and thereafter daily or hourly, as indicated. Opisthotonos appeared in from seven to twenty-four days in different pigeons. Records were also taken during the curative period of thiamine administration.

Electroencephalograms were taken without anesthesia after previous preparation of the head. This preparation consisted of the careful removal of all muscle attachments to the calvarium after reflecting the skin. Two small trephine holes were placed in the skull just to, but not penetrating, the thin inner table. These holes were bilaterally symmetric and overlay the area of junction of the forebrain, optic lobes and cerebellum. The skin was then closed over the burr holes. After this operation the electroencephalograms were taken by the use of silver–silver chloride wick electrodes applied with slight pressure and electrode jelly to the surface of the skin over these holes.[5] The head was maintained immobile by

4. Tokaji, E., and Gerard, R. W.: Avitaminosis B and Pigeon Brain Potentials, Proc. Soc. Exper. Biol. & Med. **41**:653, 1939.

5. Attempts were made first to obtain the series of electroencephalograms from electrodes placed directly in contact with various areas of the brain. Histologic study showed that damage to cerebral tissue almost invariably resulted from such procedures. It was decided that the less efficient and less well localized records obtained without exposing the brain were probably more desirable than those entailing the complication of damage to cerebral tissue resulting from any attempt to keep electrodes directly in contact with the brain for repeated examination. Control studies with needle electrodes in the optic lobes or forebrain showed records similar in all essential respects to those taken from skin surface leads over burr holes in the skull. Simultaneous photographic and ink writer records compared

solid attachment of the beak and ear plugs, all of which were attached to the frame holding the electrodes.

RESULTS

Normal pigeon brain potentials, taken in the aforedescribed manner, without anesthesia, had a predominant regular frequency of 25 to 35 per second, irregularly intermingled with which were occasional slower and faster waves. The amplitude of this predominant rhythm was normally between 10 and 40 microvolts. Slower regular waves of larger amplitude (not due to artefacts) were obtained only in thiamine-deficient pigeons or in those whose brains had been damaged by operative procedures.

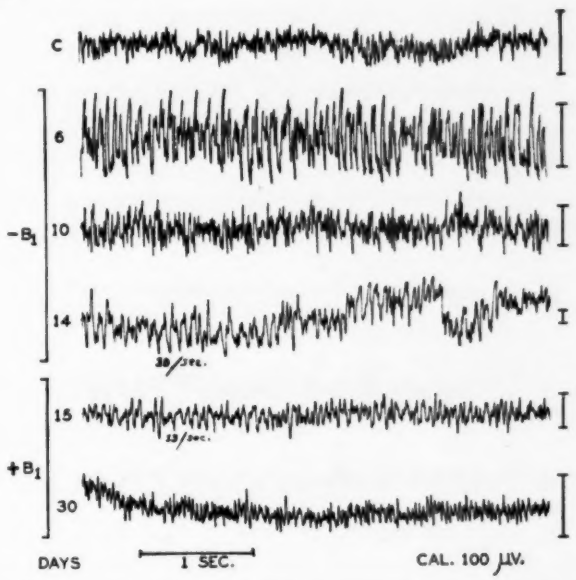

Fig. 1.—Pigeon brain potentials during progressive vitamin B_1 deficiency and recovery. *C* is a typical record from a normal pigeon. The second line shows increase in amplitude after six days of deficiency diet, at which time the first evidence of deficiency, vomiting, was present. The ten day record, taken with reduced amplification, shows activity during preopisthotonos and just before beginning opisthotonos. At fourteen days the pigeon had shown severe opisthotonos for two days, and was near enopisthotonos. Thiamine hydrochloride (200 micrograms) was then administered. The fifteen day record was taken twenty-four hours after administration of thiamine. Note the increase in frequency of the predominant rhythm. The electroencephalogram was not completely normal, as in the last line, until the thirtieth day, or after fifteen days of normal diet.

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favorably except for the high frequencies (about 200 per second) from the cerebellum, which did not show up in the ink writer records. Simultaneous records of the neck muscle potentials were taken throughout to control possible artefacts from this source. Artefacts due to eye movements were also ruled out by careful observation.

After the pigeons had consumed the deficient diet for six to ten days, at a time when vomiting and increasing nervousness were usually present, a notable increase in the amplitude of brain potentials developed slowly. Shortly before the appearance of preopisthotonos the amplitude of these potentials became three times as high as that obtained during the control period (fig. 1). With this increase in amplitude there was either a slight decrease or no appreciable change in the frequency of predominant rhythms. With the development of preopisthotonos (in eleven to fourteen days) the rhythm of the brain waves became distinctly irregular, with the appearance of slower waves intermingled with normal or faster than normal rhythms (fig. 1, ten day record). At this time

Fig. 2.—Paroxysmal epileptiform waves after seventeen days of a deficiency diet; an unusual record.

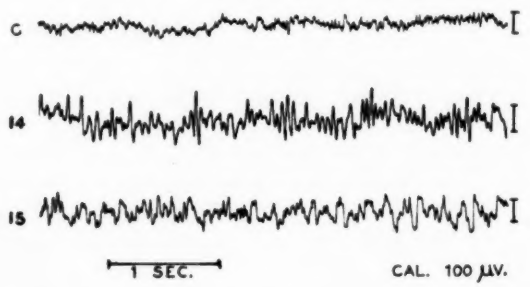

Fig. 3.—Changes in brain potentials during the control period (*C*), after three days of severe opisthotonos following fourteen days of a deficiency diet (*14*) and during enopisthotonos on the fifteenth day (*15*). This pigeon died thirty minutes after this last record was taken, in spite of administration of thiamine. Note the increased amplitude, as well as the decreased frequency, of waves during opisthotonos and the greatly reduced frequency of the brain waves (to about 7 per second) and some reduction in amplitude during enopisthotonos.

the amplitude of the brain waves had decreased, but was still greater than in the control records. These changes correlated with the appearance of the first histologic changes in the vestibular system. Large spikelike epileptiform discharges were also observed, as reported by Tokaji and Gerard.[4] Sudden paroxysmal epileptiform waves, an example of which is shown in figure 2, were observed only transiently in a few pigeons during the early part of preopisthotonos.

During opisthotonos, if thiamine was not administered the brain potentials gradually decreased in frequency to approximately 16 to 20

per second, the amplitude remaining about the same as during preopisthotonos. Occasional short bursts of normal and irregular rhythms were still present (fig. 1, fourteen day record, and fig. 3, fourteen day record). With the development of enopisthotonos the rhythm further slowed to between 7 and 14 per second and the amplitude also decreased. Also, the bursts of faster waves were much less frequent and often absent (fig. 3, fifteen day record). At this stage the pigeon often died in spite of large doses of thiamine hydrochloride.

Histologic studies (Swank and Prados [3]) on birds with mild opisthotonos revealed moderate damage to the peripheral terminations of the vestibular nerves in the labyrinths, especially to the posterior cristae, and similar changes in the nucleus magnocellularis, Deiters' nucleus, the reticular formation and other central terminations of the vestibular nerves. Also, many basket cells in the cerebellums of these birds were degenerating. In the extreme phase of the deficiency, enopisthotonos, the degeneration in both the peripheral and the central terminations of the vestibular nerves was extreme, and, as noted before, degeneration had also appeared in many other parts of the brain, especially the optic lobes, the cerebellum and the nucleus rotundus of the thalamus.

The administration of thiamine to pigeons with symptoms of preopisthotonos caused return of the brain waves to normal in a few days. In pigeons with enopisthotonos, although a change toward normal was apparent in twenty-four hours, fifteen to seventeen days of normal or experimental diet plus thiamine hydrochloride was necessary before the electroencephalograms were normal (fig. 1).

COMMENT

The increase in amplitude of brain potentials in pigeons with thiamine deficiency is in accord with the previous observations of Tokaji and Gerard. This, together with the occasional record of paroxysmal discharges of epileptiform character, indicates that during certain stages of thiamine deficiency brain discharge is facilitated.

The marked slowing of pigeon brain rhythms at extreme stages of thiamine deficiency probably indicates a final depression of brain function. This is borne out by the clinical signs of relaxation and inactivity during this period (enopisthotonos).

This initial facilitation and final depression of brain activity with progressive thiamine deficiency is similar to that observed over a much shorter time in cases of acute oxygen deficiency (Sugar and Gerard [6];

6. Sugar, O., and Gerard, R. W.: Anoxia and Brain Potentials, J. Neurophysiol. **1**:558, 1938.

Jasper, Swank and Cipriani[7]). The convulsions followed by coma in certain patients with low blood sugar due to therapeutic administration of insulin is another parallel phenomenon. It appears that a form of mass discharge of the brain is facilitated during the initial stages of metabolic deficiency, before general depression of activity takes place. This facilitation refers, of course, not to the normal integrated activity but probably to hyperirritability resulting in abnormally large synchronized discharges of central neurons.

The marked increase in amplitude with little initial change in frequency during the early stages of thiamine deficiency probably indicates that the tendency for slow waves to appear with decreased efficiency of metabolism is counteracted by the increased irritability of central neurons. Perhaps this is related to the general nervousness and tendency to vomit which is present at this time. The fact that the electroencephalogram does not show a uniform change but presents an increasing relative preponderance of slow frequencies, the rapid frequencies remaining to some extent even in cases of extreme deficiency, suggests a selective effect; the function of some neurons is more involved than others. This is in accord with the pathologic studies, which show patchy rather than uniform degeneration of neurons.

One other factor, progressive deafferentation as a result of progressive degeneration of the vestibular and other sensory systems, must be considered. Its importance in the production of the changes just described is highly problematic. Possibly it facilitates synchronized discharge.

CONCLUSIONS

Pigeon brain potentials have been recorded during various stages of vitamine B_1 deficiency and compared with records taken during control periods before and after institution of the specific deficiency diet.

1. Thiamine deficiency caused a progressive increase in amplitude of brain potentials to as much as three times the normal value. This change was apparent in the electroencephalogram before clinical signs developed.

2. During opisthotonos the brain potentials not only were of large amplitude but showed a complex change in frequency with lower frequencies becoming more prominent. The change in frequency was not uniform but seemed to indicate selective action on certain groups of neurons. This was corroborated by histologic study.

3. In some pigeons paroxysmal epileptiform waves appeared during a certain stage of the deficiency syndrome.

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7. Jasper, H. H.; Swank, R. L., and Cipriani, A.: Local Cerebral Blood Flow, p_H, and Electrical Activity During Hyperventilation, Anoxemia and Anemia, unpublished data.

4. During enopisthotonos the rapid frequencies largely disappeared, leaving relatively slow waves to characterize the entire record.

5. The brain potentials changed toward normal a few hours after administration of thiamine, but if extreme deficiency had developed the electroencephalogram did not return completely to normal until after ten to seventeen days of normal diet.

It is suggested that the changes in brain potentials indicate marked facilitation of cortical discharge during the initial phases of thiamine deficiency, before its final depression. This type of effect is compared to that of oxygen and dextrose deficiency, in which similar changes in brain potentials occur.

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PERIARTERITIS NODOSA

A CLINICOPATHOLOGIC REPORT, WITH SPECIAL REFERENCE TO THE CENTRAL NERVOUS SYSTEM

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The manifestations produced by periarteritis nodosa in the muscles, skin, peripheral nerves and various internal organs have been described previously, but there is little information available on the involvement of the central nervous system. It is our purpose to report a case presenting multiple neurologic changes and to compare our observations with those in similar cases in the literature.

REPORT OF A CASE

G. A., a white married man aged 43, was admitted to the University Hospital on Sept. 3, 1939, with a history of progressive ease of fatigue, pain in the legs, evening edema of the ankles, blurring of vision, diplopia and nocturia of eight months' duration.

On examination he appeared poorly nourished and chronically ill. The temperature was 99.6 F., the pulse rate 100, the respiratory rate 24 and the blood pressure 124 systolic and 80 diastolic. The right pupil was larger than the left, but both reacted normally to light and in accommodation. There were paresis of the medial and inferior rectus muscles on the right and equivocal paresis of the superior oblique muscle bilaterally. Nystagmus was present on lateral gaze to either side. The deep tendon reflexes were equal and hyperactive, with abortive ankle clonus bilaterally, but there was no Babinski response. There was generalized muscle tenderness, particularly marked in the calves. The Kahn reaction of the blood was weakly positive. All examinations of the blood and urinalysis gave normal results and roentgenograms of the skull and an electrocardiogram showed nothing significant. The data on the cerebrospinal fluid are included in table 1. A diagnosis of periarteritis nodosa was established by a biopsy of the gastrocnemius muscle. The symptoms remained unchanged during the ensuing two weeks. After a course of sulfanilamide the temperature returned to normal, and the muscle tenderness and diplopia disappeared.

Except for weakness, he remained asymptomatic until Dec. 1, 1939. At that time pain in the right shoulder, radiating into the right hand, and burning and

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Read at the Twentieth Annual Convention of the Central Neuropsychiatric Association, Ann Arbor, Mich., Oct. 25, 1941.

tingling sensations in the left hand appeared. There was, however, no objective evidence of peripheral neuritis. The right pupil was larger than the left, and signs of meningeal irritation in the form of nuchal rigidity and a bilateral Kernig sign were present. When next seen, on Jan. 17, 1940, the patient had been having severe bifrontal headaches for one month. The pain and paresthesias in the upper extremities persisted, the pain in the legs recurred and gaseous eructations with epigastric pain were experienced. Stumbling gait and difficulty in initiating micturition appeared shortly before admission. On reexamination, he was distinctly euphoric, and his speech was slurred. Signs of meningeal irritation were still present. There were diminished ocular convergence and abortive nystagmus. In addition to the generalized muscular weakness there was superimposed left hemiplegia, characterized by central facial paresis, spasticity of the arm and leg and hyperactive deep tendon reflexes. The abdominal reflexes were absent. The abdomen was diffusely tender on palpation. The blood pressure was 142 systolic and 94 diastolic. Examination of the urine revealed nothing abnormal. During the course of the next few weeks the mental changes progressed, the patient becoming

TABLE 1.—*Data on the Cerebrospinal Fluid*

Date	Pressure, Mm. of H_2O	Cells per Cu. Mm.	Polymorphonuclears, per Cent	Lymphocytes, per Cent	Red Blood Cells, per Cent	Total Protein, Mg./100 Cc.	Kahn Reaction	Colloidal Gold Curve
9/15/39	90	30		100		167	Negative	0001221000
12/ 8/39	160	56		100		174	Negative	0001221000
1/17/40	260	56		30	70	Xanthochromic fluid		
1/22/40	220	18	60	40		138	Negative	0012210000

garrulous and circumstantial; attention was difficult to maintain, and perception was limited. The dysarthria increased; progressive dysphagia developed; muscular wasting appeared, and central facial paralysis developed also on the right side. Serial blood counts showed progressive secondary anemia and leukocytosis, with preponderance of polymorphonuclears; there was no eosinophilia. The Kahn test of the blood persistently gave weakly positive reactions. The results of repeated examinations of the cerebrospinal fluid are shown in table 1.

Throughout the last period of hospitalization the temperature, pulse rate and respiratory rate were elevated. Death occurred on February 8, from bronchopneumonia; the duration of the disease was approximately thirteen months.

Necropsy.—Postmortem study revealed numerous small necrotic foci disseminated throughout the central nervous system, several infarcts in the kidneys, a hemorrhage in the medulla of the left adrenal gland, chronic gastric and duodenal ulcers and terminal bronchopneumonia. All the large arteries in the brain and internal organs were normal.

Microscopic Examination.—There was widespread inflammation of the small arteries and arterioles, most severe in the central nervous system and less so in the peripheral nerves, muscles, kidneys, adrenal glands, gastrointestinal tract,

mesentery, pancreas, gallbladder, liver, ureters, urinary bladder, prostate, testes, thyroid, thymus lymph nodes, vasa vasorum of the aorta and pulmonary artery, bone marrow and skin. Only the heart, lungs and spleen were spared. Acute and chronic vascular lesions were everywhere present side by side.

Acute Vascular Lesions: The acute reaction was characterized by a homogeneous ring between the intima and the media and by infiltration of the adventitia (fig. 1 *A*). The ring consisted of a "fibrinous" substance, which stained deep blue with the Weigert stain for fibrin, yellowish brown in Van Gieson preparations, greenish blue in Nissl preparations and bright red with the azan stain. A combined Weigert elastica–Van Gieson stain showed that this ring invariably occupied the subendothelial layer but frequently extended into the elastica interna and the inner portion

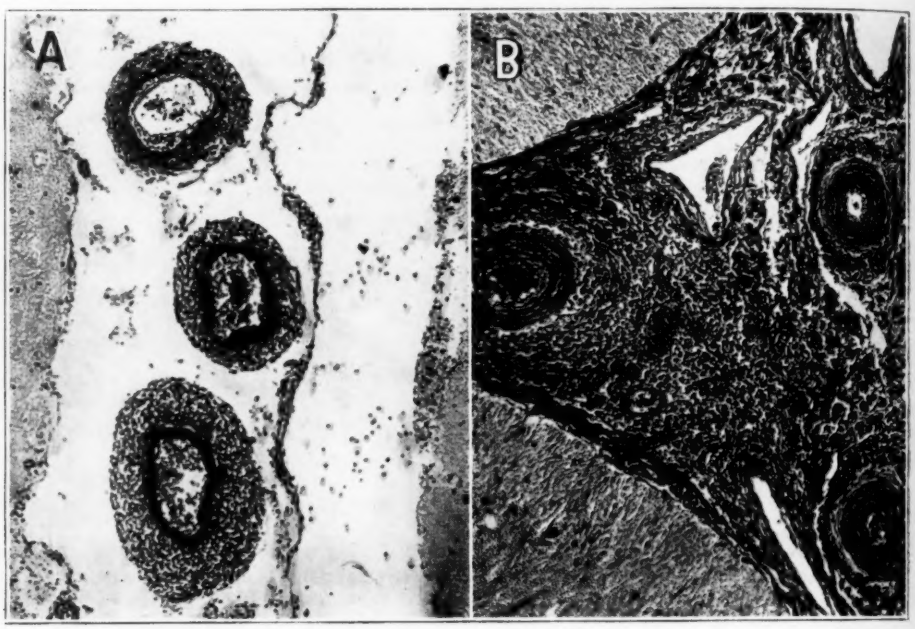

Fig. 1.—*A*, small meningeal arteries of the cerebellum in the acute phase of periarteritis nodosa, characterized by a homogeneous fibrin ring in the subintima and by infiltration of the adventitia with lymphocytes and plasma cells. The outer portion of the media is relatively preserved. Azan stain; Zeiss objective, 16 mm.; ocular no. 2.

B, lesions affecting small meningeal arteries of the spinal cord in the chronic phase, characterized by subintimal thickening, restoration of the elastica interna, diffuse degeneration of the media and fibrosis of the adventitia; subacute meningitis. Van Gieson–Weigert elastica stain; Zeiss planar lens, 20 mm.

of the media, partly obscuring the latter structure. Thus, the ring was enclosed between a swollen, though intact, endothelium and the external layer of the media. The adventitia was densely infiltrated with lymphocytes, plasma cells and some polyblasts; a few of these cells penetrated the deeper structures of the vessel wall.

Chronic Vascular Lesions: The chronic stage was characterized by disappearance of the homogeneous ring and advanced organization (fig. 1 *B*). The intima was markedly thickened, and the lumen was narrowed or obliterated by connective tissue. There was complete or partial restoration of the elastica interna. The media usually remained visible but stained poorly, owing to degeneration of the myofibrils, and showed some compensatory fibrosis. The adventitia was noticeably thickened but no longer infiltrated. There were numerous lesions in transitional stages of organization, the fibrin ring frequently appearing fenestrated before it was completely resorbed. Many vessels contained thrombi, some of them recent and others in various stages of organization, but no aneurysms. The small veins occasionally showed similar changes, although usually only infiltration of the adventitia.

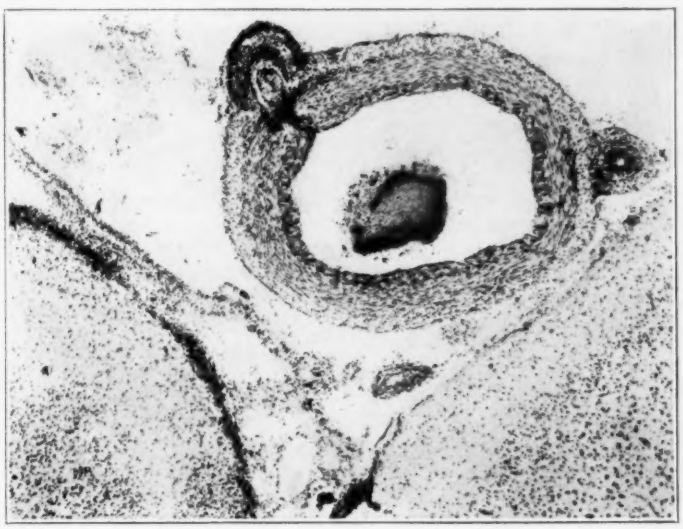

Fig. 2.—Vascular lesions in the meninges of the cerebral cortex, involving two small branches of a larger artery which is intact; patchy meningitis, and marginal proliferation of glia. Nissl stain; Zeiss planar lens, 20 mm.

The disease reached its greatest intensity in the central nervous system, the most constant change occurring in the meninges and the adjacent marginal zones. Only the small meningeal arteries were affected (fig. 2), showing lesions in all stages of development, while in the meshes of the pia-arachnoid there were patchy infiltrations of lymphocytes, plasma cells and polyblasts. As the meningeal vessels entered the marginal zones of the brain, the vascular lesions were frequently surrounded by focal accumulations of gitter cells, microglia cells and astrocytes, accompanied by diffuse proliferation of the glia. Within the cerebral cortex infarcts, varying in age from recent anemic foci to softenings containing fat-laden gitter cells and astrocytes, as well as areas of "paling," with poorly stained parenchyma, were common; these were largely related to occluded vessels in the meninges (fig. 3). Perivascular hemorrhages were less common. Scattered arterial lesions

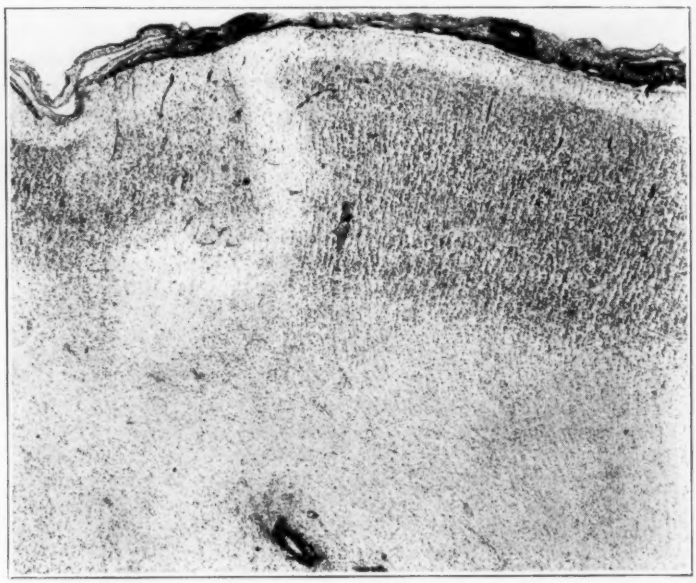

Fig. 3.—Recent infarcts in the cerebral cortex related to thrombosed vessels in the overlying meninges; disseminated vascular lesions in the white matter. Nissl stain; Zeiss planar lens, 50 mm.

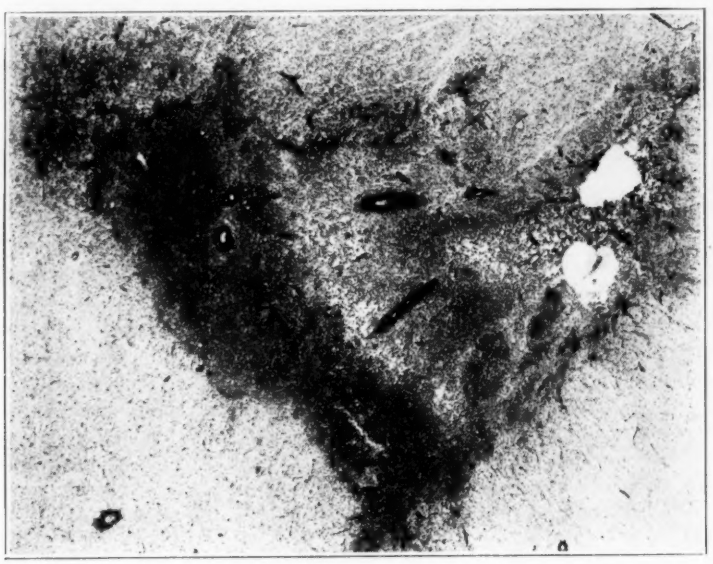

Fig. 4.—Large area of softening, composed of gitter cells and inflamed blood vessels, in the right globus pallidus. Nissl stain; Zeiss planar lens, 50 mm.

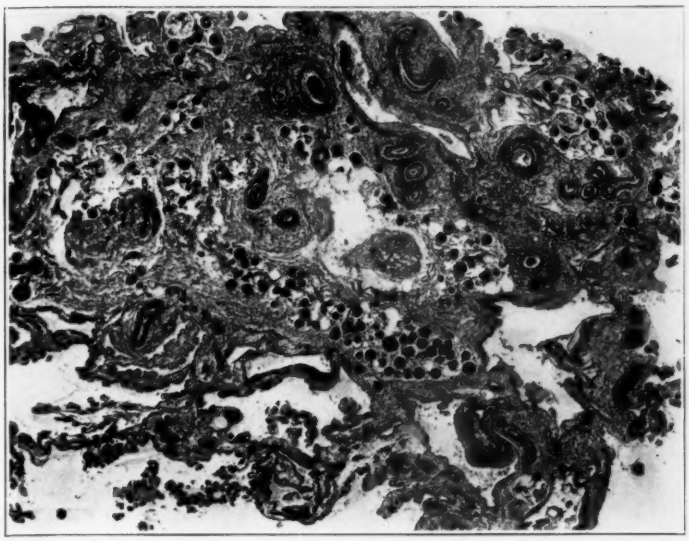

Fig. 5.—Numerous vascular lesions, in various stages of development, in the choroid plexus. Van Gieson–Weigert elastica stain; Zeiss planar lens, 20 mm.

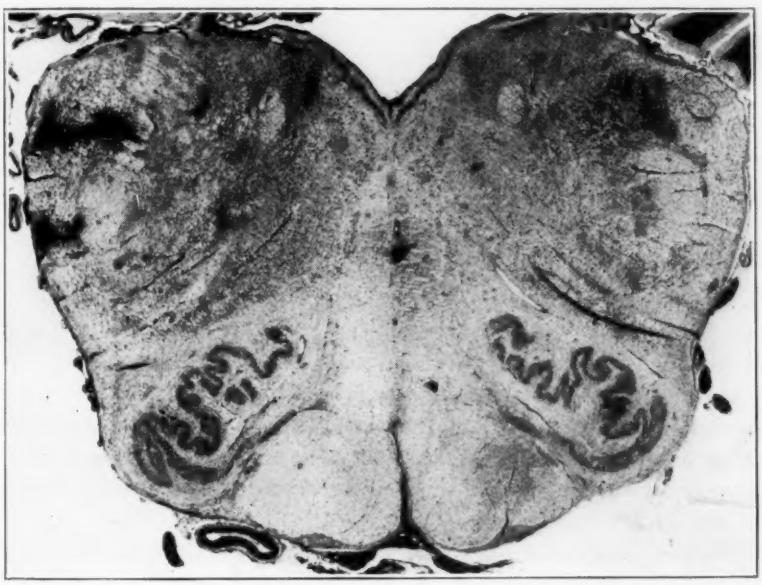

Fig. 6.—Vascular lesions in the medulla, predominantly in the meninges and marginal zones with perivascular foci of softening in the restiform body and lateral cuneate and lateral reticular nuclei, extending into the reticular substance, and diffuse gliosis of the peripherally situated cranial nuclei. Nissl stain; 10.5 lens × 5.

with perivascular softenings or glial scars were observed in the cerebral white matter, corpus callosum, thalamus and hypothalamus. There were extensive bilateral softenings in the globus pallidus (fig. 4), whereas the corpus striatum was least involved. The choroid plexus contained numerous vascular lesions of all stages (fig. 5). In the brain stem the marginal change was especially severe, resulting in involvement of the more peripherally situated structures, such as the geniculate and quadrigeminal bodies, the restiform body and the lateral reticular, lateral cuneate, trigeminal, facial, vestibular and acoustic nuclei (fig. 6). More centrally located lesions were noted in the oculomotor nuclei, the reticular formation and the basilar portion of the pons. In the cerebellum there was diffuse glial proliferation in the dentate nuclei and in the gyral white matter, while focal outfalls of Purkinje cells with reacting glial "shrubberies" were occasionally seen. At

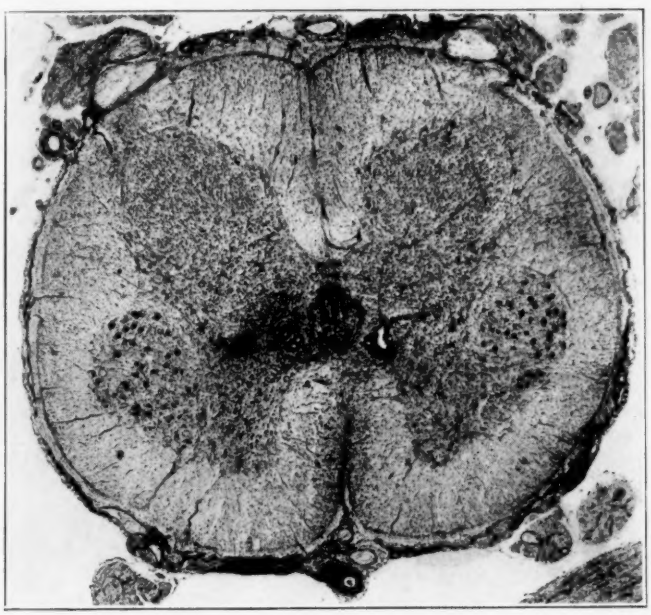

Fig. 7.—Vascular lesions in the meninges and vicinity of the central canal of the spinal cord, with perivascular foci of gliosis; patchy meningitis, and diffuse marginal gliosis in the white matter. Nissl stain; Zeiss planar lens, 50 mm.

various levels of the spinal cord (fig. 7) there were constant marginal involvement, numerous lesions in the vicinity of the central canal and scattered foci in the lateral and posterior columns, while the gray columns showed only axonal reaction changes in the anterior horn cells.

In the peripheral nerves (only small segments of the brachial and lumbosacral plexuses were examined) numerous vascular lesions involved the small arteries in the perineurium (fig. 8*A*), but the nerve fibers at the same level showed relatively little degeneration. The muscles (fig. 8*B*) likewise contained numerous vascular lesions and only patchy degeneration of adjacent muscle fibers. The kidneys showed

scattered infarcts corresponding to vascular lesions of various stages. In both adrenal glands there were numerous vascular lesions, with a recent hemorrhagic infarct, due to thrombosis of the central vein, in the medulla of the left gland. The remaining organs showed typical changes of periarteritis nodosa, affecting predominantly the arterioles in the capsules of the organs, in the subserosa and submucosa of the gastrointestinal tract and in the subcutaneous tissue, without producing any infarcts. Examination of the brain and various organs for spirochetes gave negative results.

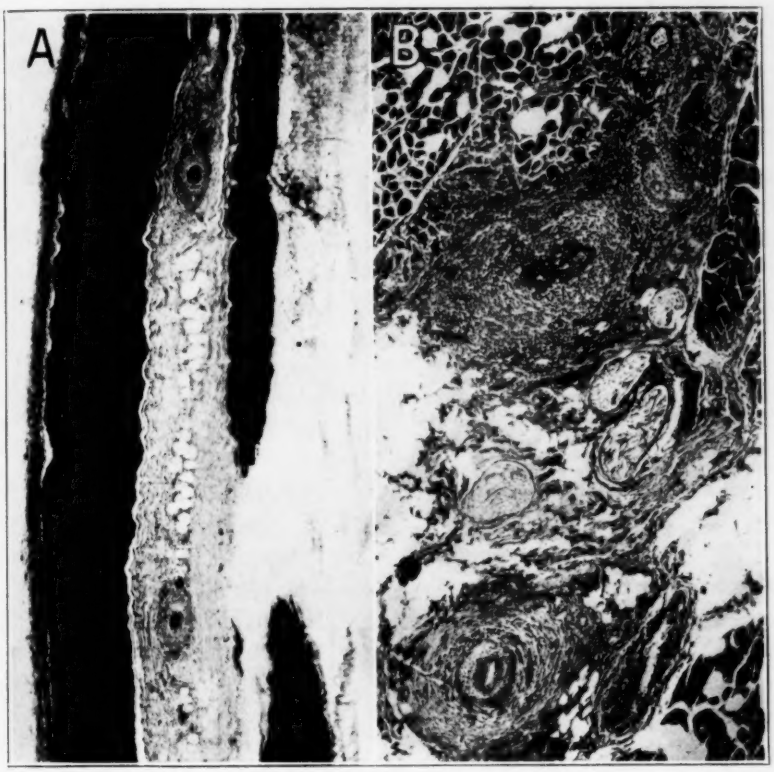

Fig. 8.—*A*, peripheral nerve, showing vascular lesions in perineural sheaths but preserved nerve fibers at this level. Spielmeyer stain; Zeiss planar lens, 50 mm.

B, vascular lesions in muscles, with patchy degeneration of adjacent muscle fibers. Azan stain; Zeiss planar lens, 20 mm.

COMMENT

Incidence.—The incidence of changes in the central nervous system associated with periarteritis nodosa appears to have been underestimated. Of 300 cases that we have reviewed from the literature, clinical signs referable to the central nervous system were presented in 65, or slightly over 20 per cent. Table 2 lists the neurologic signs in order of their frequency.

This 20 per cent estimate is somewhat higher than that of either Gruber [1] or Arkin,[2] who obtained an incidence of 6 and 8 per cent, respectively. Since periarteritis nodosa may begin in the central nervous system, it is important to consider it as a diagnosis when confronted with the neurologic signs listed in table 2. In our case, the greater involvement of the central nervous system, peripheral nerves and muscles corresponded to a clinical picture in which the chief manifestations were neurologic and muscular. Such extensive involvement of the nervous system is not unique, similar cases having been reported by Runge and

TABLE 2.—*Neurologic Signs in Sixty-Five Cases of Periarteritis Nodosa*

Sign	Number of Cases	Percentage of Total Number
Convulsions, generalized	24	37
Meningeal irritation	14	22
Organic cerebral syndrome	14	22
Hemiplegia	11	17
Sluggish pupillary light reflex	11	17
Anisocoria	10	15
Cerebellar signs	9	14
Convulsions, jacksonian	8	11
Increased cerebrospinal fluid pressure	8	11
Increased cerebrospinal fluid protein	6	9
Palsies of extraocular muscles	5	8
Extrapyramidal signs	5	8
Papilledema	4	6
Optic nerve atrophy	4	6
Nystagmus	4	6
Peripheral palsy of facial nerve	4	6
Erythrocytes in cerebrospinal fluid	4	6
Subarachnoid hemorrhage	3	5
Lymphocytic increase in cerebrospinal fluid	3	5
Nerve deafness	2	3
Hypoglossal palsy	2	3
Decerebrate rigidity	2	3
Pseudobulbar palsy	2	3
Visual hallucinations	2	3
Ramsay Hunt syndrome	1	2
Polymorphonuclear increase in cerebrospinal fluid	1	2
Transverse myelitis	1	2

Melzer,[3] Richardson,[4] Urechia and Elekes [5] and other authors. Although isolated involvement of the nervous system may occur (Richardson,[4]

1. Gruber, G. B.: Kasuistik und Kritik der Periarteriitis nodosa, Zentralbl. f. Herz- u. Gefässkr. **18**:145, 1926.

2. Arkin, A.: A Clinical and Pathological Study of Periarteritis Nodosa, Am. J. Path. **6**:401 (July) 1930.

3. Runge, W., and Melzer, R.: Ueber Periarteriitis nodosa mit starker Beteiligung des Zentralnervensystems, J. f. Psychol. u. Neurol. **40**:298 (May) 1930.

4. Richardson, M.: Läsionen des Zentralnervensystems bei Periarteriitis nodosa, Ztschr. f. d. ges. Neurol. u. Psychiat. **115**:626, 1928.

5. Urechia, C. I., and Elekes, N.: Les formes nerveuses de l'artérite noueuse de Kussmaul, Ann. de méd. **36**:466 (Dec.) 1934.

Kernohan and Woltman [6]), it is the characteristic widespread distribution in multiple organs and systems which furnishes the clue to diagnosis, most convincingly proved by biopsy.

Pathogenesis.—It is generally accepted that the disease is an inflammatory process of the arterial system, preferring the medium-sized and small arteries, although in some cases the veins and the pia-arachnoid may also be involved. Opinions differ, however, as to whether the primary lesion is in the intima, the media or the adventitia. In our opinion, the disease is a panarteritis, since there is evidence in our case that it begins simultaneously in all three layers. The earliest change is characterized by deposition of a ring of fibrin in the subintima, the elastica interna and the adjacent part of the media and by exudation of polymorphonuclear leukocytes, lymphocytes and plasma cells in the adventitia. As the condition progresses there is gradual resorption of the ring, leaving the elastica interna wholly or partially restored and the media diffusely degenerated, while the infiltration in the adventitia begins to recede. Finally, organization of the subintima and the adventitia develops by proliferation of connective tissue to the point of healing of the lesion. Such a sequence of events applies at any rate to the involvement of the smaller arteries. According to Gruber,[7] when larger arteries are affected, the process begins between the adventitia and the media and then progresses inward. Another controversial point in the literature is the manner in which the parenchymal changes are produced. Although it is conceded that the vascular lesions can bring about such changes directly through occlusion by intimal proliferation and thrombosis or through a ruptured aneurysm, a toxic factor is also assumed by some authors (Wohlwill,[8] Baló,[9] Silbermann [10] and others). This is inferred from an apparent lack of parallelism between the degree of involvement of the vessels and the degree of damage to the tissues, as well as from the frequent diffuse character of the changes. Recently, however, Kernohan and Woltman,[6] after thorough examination of the peripheral nerves along their entire course, proved beyond any doubt that a direct relation exists between involvement of nutrient arteries and damage to the

6. Kernohan, J. W., and Woltman, H. W.: Periarteritis Nodosa: A Clinicopathologic Report with Special Reference to the Nervous System, Arch. Neurol. & Psychiat. **39**:655 (April) 1938.

7. Gruber, G. B.: Zur Frage der Periarteriitis nodosa, mit besonderer Berücksichtigung der Gallenblasen- und Nieren-Beteiligung, Virchows Arch. f. path. Anat. **258**:441, 1925.

8. Wohlwill, F.: Ueber die nur mikroskopisch erkennbare Forme der Periarteriitis nodosa, Virchows Arch. f. path. Anat. **246**:377, 1923.

9. Baló, J.: Maladie de Kussmaul-Maier et sclérose diffuse, J. belge de neurol. et de psychiat. **40**:160 (March) 1940.

10. Silbermann, J.: Zur Klinik und pathologischen Histologie der Periarteriitis nodosa, Monatschr. f. Psychiat. u. Neurol. **72**:225 (June) 1929.

parenchyma. It is obvious that in the case of such a disseminated disease serial studies are necessary to demonstrate this parallelism. Moreover, the presence of vascular lesions does not necessarily signify that tissue changes will occur, since these result only from occlusion of vessels. Thus, in our case, although arterial lesions were widespread, only a few organs showed parenchymal changes. These consisted essentially of infarcts of various ages, corresponding to the stages of the vascular lesions. In the central nervous system the associated diffuse ischemic changes and marginal gliosis were apparently determined by the adjacent vascular and meningeal involvement. It is for these reasons that we regard periarteritis nodosa as purely a vascular disease.

Our investigation contributes no information as to the cause of the disorder, and we agree with most authors that periarteritis nodosa is an inflammatory condition but has nothing in common with syphilis. The positive serologic reactions for syphilis in our case were not supported by any historical, clinical or pathologic evidence. Similar observations have been noted by Harris and his co-workers [11] in 8 per cent of 101 reported cases. It would seem that periarteritis nodosa is prone to cause false positive serologic reactions. Antisyphilitic treatment has not been efficacious. It is possible that sulfanilamide was important in producing the remission in our patient, and a further trial of this drug seems warranted in view of the absence of other specific therapy at present and the generally unfavorable course of the disease.

SUMMARY

A case of periarteritis nodosa with predominantly neurologic manifestations is reported. It is emphasized, from a review of the literature, that involvement of the central nervous system in this disorder is not uncommon.

Pathogenetically, the condition is regarded as panarteritis and the parenchymal changes as of vascular origin.

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11. Harris, A. W.; Lynch, G. W., and O'Hare, J. P.: Periarteritis Nodosa, Arch. Int. Med. **63**:1163 (June) 1939.

SPECIAL ARTICLE

SOME PROBLEMS OF WARTIME NEUROLOGY

WILDER PENFIELD, M.D. D.Sc.
MONTREAL, CANADA

The sound of marching feet across the Polish frontier in 1939 changed the world in which we lived, we who lived in the British empire. Exploding bombs in Pearl Harbor altered the outlook of the rest of the people in the world who use the English tongue. Although one may recognize that one's world has changed, it is not immediately evident to the individual what his own particular reorientation may be, where his own talents may be applied.

Conscription and the training of troops who will march or sail away form only one aspect of war today. We, who have thought so little about war, are apt to have a rather hazy medieval conception that it signifies only a situation in which soldiers depart on a crusade which is carried through by an inevitably rising tide of patriotism. This point of view ignores the fact that today a civilian war must also be declared and the final issue may turn on its outcome.

Science itself has brought about a great change. It has altered society, made the world small, armed the aggressor mightily and finally brought one civilian population face to face with another civilian population in a war of labor, of self denial and of wits. In such a war as this, one might reasonably expect the scales to be tipped by weight of native wit and scientific resource. To do this, men and women of every way of life must toss their particular talents on the balance.

What role can the neurologist play? What are his problems? What value his specialized knowledge? Sir Charles Sherrington worked in a munitions factory for a time during the last war. That should be unthinkable in this war. There is work in plenty for such a mind. The key men in the various medical committees of the research councils of Britain, Canada and the United States are physiologists.

A clinician who wants to contribute should assess for himself those problems in his own field which are of importance in this struggle, and

From the Departments of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

This paper formed part of an address delivered before the Boston Society of Psychiatry and Neurology, March 19, 1942.

then turn his back on other problems during the war years. There is no sovereign technic to lead one to important discovery. Pasteur said of invention only that "chance favours the prepared mind." Consequently, one can but direct one's attention toward the essential problems and hope for the best.

In the Neurological Institute with which I am associated in Montreal a decision was made by all the staff that research should be abandoned except for those investigations which seemed to have some bearing on the military and civilian problems of this struggle. This voluntary reorientation was made only after war had been under way for some time, later than it should have been, because of our own preoccupations and our initial failure to appreciate the new role that medicine might play. Nevertheless, whatever may be its outcome, work is now going forward on such subjects as the neurophysiology of experimental acceleration ("blackout"), motion sickness, cerebral edema, prevention of meningocerebral adhesions, traumatic headache, the psychoneurotic personality pattern and chemotherapy against contamination and infection of the intracranial spaces.

Last autumn I took off in a bomber and ten hours later dropped down through the clouds over a peaceful British countryside, with its orderly hedgerows and grazing cattle. The purpose of my visit was to make a report on clinical problems to the Medical Research Committee of the National Research Council at Ottawa. The single problem which, it seemed to me, might well prove to be of paramount importance was the treatment of burns by simple methods, methods which call for a minimum of time and labor. If I now presume to enumerate problems in which this society might be expected to take an especial interest, the suggestions should be accepted only as the expression of a personal opinion.

Suitable subjects for research which seem to come within the ken of neurologist and neurosurgeon, and those psychiatrists who have psychologic and physiologic leanings, are the following problems: (*a*) methods of selection of military personnel, including intelligence tests, aptitude tests and personality studies; (*b*) the making of morale among men in service and among the families left behind; (*c*) prevention and relief of fatigue; (*d*) prevention and cure of psychoneurosis; (*e*) effects of blast on the nervous system; (*f*) nerve suture and nerve regeneration; (*g*) analeptic substances; (*h*) immersion foot and vascular occlusion; (*i*) prevention of adhesions about the brain and nerves; (*j*) treatment of cerebral and meningeal infections; (*k*) treatment of craniofacial injuries; (*l*) transportation and treatment of patients with spinal fractures and dislocations; (*m*) post-traumatic headache; (*n*) post-traumatic epilepsy;

(*o*) post-traumatic circulatory instability; (*p*) pain in the lower part of the back; (*q*) treatment of the paralyzed bladder, and (*r*) treatment of infections of the nervous system. This is to enumerate but a few fields in which there is room for improvement.

It should be recognized as a principle in a democratic country that the government cannot be considered omniscient, or always wise. Leadership must therefore develop spontaneously in every department of national life. New ideas and new efforts should break out among men in all walks of life, from laborer to industrialist and professor, like an epidemic of influenza.

3801 University Street.

News and Comment

A CALL TO QUALIFIED PSYCHIATRIC SOCIAL WORKERS BY THE AMERICAN RED CROSS

The American Red Cross is responsible for social service in Navy and Army general and station hospitals, both here and abroad, and in psychiatric units in Navy and Marine Corps training stations. Psychiatric social workers are needed for the psychiatric services in these hospitals and units and may also be used as field directors in general hospitals and assistant field directors in station hospitals.

This psychiatric service is largely concerned with diagnosis and military disposition. The psychiatric social worker, through Red Cross channels, provides the psychiatric social history and assists with the patient's readjustment after discharge through interpretative letters to the Red Cross chapter in his home community.

Salaries range from $150 to $225 per month, depending on the qualifications of the worker and her responsibilities. For foreign assignments the salary is $225 plus $45 for flat maintenance, transportation and insurance, irrespective of location.

All types of positions call for the personal qualifications of adaptability, tact, dignity, graciousness, racial and religious tolerance, a well groomed and attractive appearance and unquestioned loyalty to the United States. The number of such workers desired can only be an estimate and will depend on military developments, and requirements of training and experience will be determined by the needs and how they can be met.

Applications for foreign service should be addressed to the Director of Personnel, American National Red Cross, Washington, D. C., and for service in this country, to the directors of personnel in the following area offices: Eastern Area, A. R. C., 615 North Saint Asaph Street, Alexandria, Va.; Midwestern Area, A. R. C., 1709 Washington Avenue, St. Louis; Pacific Area, A. R. C., Civic Auditorium, San Francisco.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

VITAMIN A DEFICIENCY AND THE NERVOUS SYSTEM. S. B. WOLBACH and OTTO A. BESSEY, Arch. Path. **32**:689 (Nov.) 1941.

Wohlbach and Bessey report the results of an experimental study of vitamin A deficiency, chiefly on white rats, with confirmatory observations on guinea pigs and dogs. The literature indicates that vitamin A deficiency in the young of several mammals and in fowls results in damage to the central nervous system. Wohlbach and Bessey suggest that in all vertebrates the common sequence is that of disproportionate growth. They predict that acute, uncomplicated vitamin A deficiency in the human infant would produce similar results.

They conclude that the nervous lesions of vitamin A deficiency are wholly of mechanical origin, the genesis of which is a disproportionate growth of the central nervous system in relation to the bone which surrounds it.

Two conspicuous consequences of the disproportionate growth are noted: (1) Overcrowding of the cranial cavity, resulting in distortion of the brain, dislocation toward the foramen magnum, with herniation of the cerebellum therein, and multiple herniations of the cerebrum and cerebellum into the venous sinuses of the dura at sites of arachnoid drainage structures. (2) Overcrowding of the spinal canal, with distortion of the spinal cord and herniations of nerve roots into intervertebral foramens and into bodies of vertebrae.

In vitamin A deficiency in young animals the normal growth rate of the central nervous system is maintained until the effects of general inanition as shown by a decided retardation of gain in weight of the animal as a whole become apparent. Also, the regenerative power of the axons and presumably their physiologic potentialities are not impaired.

The early retardation of growth of bone is suggestive of a specific effect which, because of histologic observations, is probably chiefly operative in the cartilage of the epiphyses. The vis a tergo of osteogenesis per se is not lost, and possibly not impaired, before the period of general inanition is reached, as suggested by the changes in pitted vertebrae and in regions adjacent to the periotic bony capsule.

WINKELMAN, Philadelphia.

EFFECT OF AMPHETAMINE (BENZEDRINE) ON FATIGUE OF THE CENTRAL NERVOUS SYSTEM. ERNST SIMONSON, NORBERT ENZER and S. S. BLANKSTEIN, War Med. **1**:690 (Sept.) 1941.

In 62 experiments on 6 subjects occupied in types of work without muscular effort it was found that fatigue of the central nervous system consistently decreased the fusion frequency of flicker. This indicates a decrease of the excitability of, at least, the retinocortical system, and probably of the whole central nervous system, in fatigue. Amphetamine sulfate given three and one-half hours before the end of the working day increased the fusion frequency of flicker, the increase paralleling the abolition of the sense of fatigue. This indicates that the abolition or reduction of the sense of fatgue after the use of amphetamine not only is a subjective phenomenon but is substantiated by an increase in the excitability of the central nervous system. There is some evidence that this effect does not depend on the actual state of the central nervous system at the time when amphetamine is given.

PEARSON, Philadelphia.

TRAUMATIC SHOCK IN EXPERIMENTAL CEREBRAL CONCUSSION. D. DENNY-BROWN and W. RITCHIE RUSSELL, J. Physiol. **99**:6 P (June) 1941.

Continuing their studies on experimental concussion in animals, Denny-Brown and Russell observed a sudden fall in blood pressure after injuries calculated to cause concussion. This occurred at times within a few seconds after the injury, in which case it appeared to be the result of reflex stimulation of the vagus nerve. In cases of more severe injury complete failure of the blood pressure, which frequently proved fatal, was seen a few minutes after the injury. This secondary fall in blood pressure was not associated with asphyxia, but was interpreted as possibly analogous to "acute surgical shock."

THOMAS, Philadelphia.

THE DISTRIBUTION OF ACETYLCHOLINE IN THE PERIPHERAL AND THE CENTRAL NERVOUS SYSTEM. F. C. MACINTOSH, J. Physiol. **99**:436, 1941.

MacIntosh determined the concentration of acetylcholine in various parts of the central nervous system and in the peripheral nerves. Nerve trunks containing mainly somatic motor or preganglionic autonomic fibers are comparatively rich in acetylcholine, with values ranging from 6 to 18 micrograms per gram. The sensory nerves contain much smaller amounts, generally less than 0.5 micrograms per gram. Sympathetic ganglia contain the largest amounts, ranging up to 44 micrograms per gram. The nodose ganglion of the vagus nerve, on the other hand, contains about the same proportion of acetylcholine as the trunk of the nerve below the ganglion. In nerves allowed to degenerate for from five to eight days after section the amount of acetylcholine was reduced to from 3 to 25 per cent of that present in normal nerves. In general the amount of acetylcholine in the brain and spinal cord is less than in peripheral nerves, ranging from less than 1 to a maximum of 4.5 micrograms per gram. In the spinal cord the acetylcholine is mainly confined to the gray matter, but some is also present in the white columns through which the motor axons pass. The cerebellum contains hardly any acetylcholine.

THOMAS, Philadelphia.

SKELETAL CHANGES AFFECTING THE NERVOUS SYSTEM PRODUCED IN YOUNG DOGS BY DIETS DEFICIENT IN VITAMIN A. EDWARD MELLANBY, J. Physiol. **99**:467, 1941.

Mellanby reports an extensive investigation of the effects of vitamin A–deficient diets on the growth of bones, particularly those so situated that abnormal growth could cause changes in the nervous system. He found that vitamin A deficiency causes proliferation of cancellous bone at the expense of compact bone, causing many bones to lose their normal outline and to become thickened and enlarged. Such overgrowth in the skull and vertebral column may cause degenerative changes in the brain and in cranial and spinal nerves. The greatest hypertrophy is observed in the bones forming the posterior fossa of the skull, so that the medulla oblongata, pons, cerebellum and associated cranial nerves are especially affected. Posterior root ganglia and anterior roots of the spinal nerves may also be compressed and the nerve fibers destroyed, particularly in the cervical region. In cases of advanced changes there is a substantial increase (up to 100 per cent) in the intracranial pressure. The author suggests that many, if not all, the nerve changes resulting from vitamin A deficiency may be secondary to changes in the bones.

THOMAS, Philadelphia.

Neuropathology

MICROCEPHALY. CLEMENS E. BENDA, Am. J. Psychiat. **97**:1135 (March) 1941.

Benda reports 2 cases of microcephaly in which autopsy was performed. In the first the condition was of unknown origin. Macrogyria with microgyria interna was present, and the status of the cerebrum was that of a 6 month fetus. The age

at death was 10 years. The second case was one of microcephaly with cystic degeneration of the white matter, the result of asphyxia at birth. Death occurred at 2 years of age.

Benda points out that the hydrocephalus found in such cases is due to lack of development of the white matter of the brain. FORSTER, Boston.

CONGENITAL ANOMALY OF THE CEREBELLAR VERMIS. A. L. SAHS, Arch. Path. **32**:52 (July) 1941.

Development anomalies of the vermis of the cerebellum are rare, if one may judge from the literature. Sahs reports a case in which the signs and symptoms of a tumor of the posterior fossa were presented. A 16 year old boy who suffered from epileptic seizures and dizziness after exertion and changes in position was admitted to the hospital with acute symptoms, which had developed after a neck-strengthening contest. At operation he was observed to have what was apparently a defect of the vermis with a greatly enlarged fourth ventricle. Autopsy revealed a moderate degree of internal hydrocephalus, generalized narrowing of the sulci and flattening of the gyri and displacement and compression of the occipital lobes, the splenium of the corpus callosum and the vermis of the cerebellum. The vermis, however, was present in rudimentary form, with all its major divisions.

WINKELMAN, Philadelphia.

OSTEOGENIC SARCOMA OF MENINGEAL ORIGIN. OSCAR A. TURNER and WINCHELL MCK. CRAIG, Arch. Path. **32**:103 (July) 1941.

Turner and Craig describe an unusual intracranial tumor of meningeal origin in which active osteogenic and osteoclastic processes occurred throughout the tissue in combination with sarcomatous transformation of the intervening fibroblastic connective tissue.

The authors believe that true osteoblastic meningeal tumors are rare and that the osseous tissue in most of the so-called osteogenic tumors diagnosed as meningioma is an example of heteroplastic, or vicarious, formation of bone, secondary to the changes which cause ossification in other organs and tumors in the body.

The criterion for the osteogenic character of these meningeal tumors should be the presence of an active cellular osteoblastic process rather than the mere inclusion of bone in the tumor tissue. WINKELMAN, Philadelphia.

PSAMMOMATOUS DURAL ENDOTHELIOMA (MENINGIOMA) WITH PULMONARY METASTASIS. HARRY N. JUROW, Arch. Path. **32**:222 (Aug.) 1941.

Jurow reports the case of a 72 year old Negress without signs or symptoms of tumor of the brain. At autopsy two tumors were found attached to the dura and compressing the brain, one "at the junction of the left central and longitudinal fissures" and a smaller mass on "the lateral wall of the left middle cranial fossa." In addition, a nodule was found in the right pulmonary apex. Microscopic examination of the cerebral lesions showed "dural endothelioma of the psammomatous type." The tumor in the lung resembled to a remarkable degree the lesions in the brain.

The author concludes that in view of the fact that primary lesions of this type have not been observed in the lung and the tumors were not sarcomatous the most plausible deduction is that the lesion in the lung "was carried there via the blood stream." WINKELMAN, Philadelphia.

ANOMALIES OF THE CIRCLE OF WILLIS IN RELATION TO CEREBRAL SOFTENING. GEORGE H. FETTERMAN and THOMAS J. MORAN, Arch. Path. **32**:251 (Aug.) 1941.

Fetterman and Moran studied the anomalies of the posterior communicating branches of the circle of Willis in cases of cerebral softening. They found

abnormalities in 50 per cent of the cases. In 23 per cent of 200 cases there were "interruptive circle anomalies" involving the posterior communicating branches alone. Cerebral softening occurred in 30 per cent of the total number of brains, with a definitely higher incidence in the group showing circle anomalies.

WINKELMAN, Philadelphia.

EASTERN EQUINE ENCEPHALOMYELITIS. L. S. KING, J. Exper. Med. **71**:95 and 107, 1940.

A fresh strain of the virus of equine encephalomyelitis is infectious for adult mice in high dilutions by all modes of peripheral inoculation. A fixed strain has very limited invasive power when injected peripherally unless it is placed in fairly close contact with nerve cell bodies, as in the intranasal or the intraocular route. For fixed virus the effectiveness of the mode of inoculation may be graded in the following descending order: intracerebral, intraocular and intranasal, intravenous, intraperitoneal, intramuscular, subcutaneous. Fixed virus has a very limited power of invading the central nervous system along the axons of peripheral nerves, even when injected directly into the nerve. Infants are more susceptible to infection than are adults. But even in infants intraperitoneal inoculation with fixed virus is significantly less effective than similar inoculation with fresh virus. Trauma of the brain does not increase the effective titer of fresh or fixed viruses but may shorten the period of incubation for fresh virus. With intramuscular injection of fixed virus, a pronounced facilitating effect may be produced by simultaneous intraperitoneal injection of 0.20 to 0.25 cc. of 50 per cent glycerin. Other irritants tried are without effect.

In infant mice affected with equine encephalomyelitis the first pathologic disturbance is an inflammatory reaction; the corresponding reaction in adult animals is usually less pronounced. A characteristic type of parenchymal damage appears to be independent of the inflammation. In such foci of injury there is initially vacuolation of intercellular tissue. Neurons in such areas are at first intact; later they show cytoplasmic changes and finally nuclear alterations. Complete disintegrations of tissue and all its elements may be the end result.

FROM AUTHOR'S SUMMARY. [ARCH. PATH.]

ACUTE HEMORRHAGIC LEUKOENCEPHALITIS. E. W. HURST, M. J. Australia **2**:1 (July 5) 1941.

Hurst discusses an undefined entity that he had encountered in 2 cases and verified post mortem. The disease is an acute cerebral condition termed acute hemorrhagic leukoencephalitis. It is localized in the cerebral white matter and develops more or less abruptly in apparently normal persons. Perivascular necroses, perivascular and focal demyelination, hemorrhages, edema and cellular infiltration were the chief pathologic changes. The principal clinical feature was rapid abrogation of the higher cerebral functions in previously healthy persons associated with headache, vomiting, slight pyrexia or leukocytosis. Identical cerebral lesions were observed at necropsy in the 2 patients. The highly hemorrhagic and edematous state was localized chiefly in the white matter of the left hemisphere. Subsequent microscopic examination revealed lesions independent of as well as associated with hemorrhages and edema. They included important damage to the vascular, perivascular and intervascular tissues. There was no clearcut vascular thrombosis. Often the vascular walls were permeated by and their perivascular spaces distended with fibrin. In the nerve tissue surrounding venules and precapillaries the lesions were either of partial demyelination, with some outfall of axis-cylinders, or of changes leading up to necrosis. The association of the former with obviously less severely affected vessels situated at a distance from the most damaged areas suggests different degrees of injury by a single noxious agent. A few foci of partial demyelination apparently occurred

independent of a vessel. The intense polymorphonuclear infiltration in the perivascular spaces and in the nerve tissues bore witness to the acuteness and severity of the condition. The changes suggest an acute demyelinating disease, such as postvaccinal encephalitis, rather than a virus malady characterized by a polioclastic type of lesion. The brains were received fixed in formaldehyde-saline solution. No organisms were seen in stained sections. The author compares the lesions in his 2 cases with those encountered in cases of brain purpura and in Baker's hemorrhagic encephalitis. He suggests that acute hemorrhagic leukoencephalitis may represent a link between demyelinating diseases and some forms of "hemorrhagic encephalitis."

J. A. M. A.

MORPHOLOGIC STUDIES OF THE BLOOD VESSELS IN A GLIOMA SAID TO BE OF APOPLECTIC ORIGIN. HANS BERTHA, Ztschr. f. d. ges. Neurol. u. Psychiat. **169**:617 (June) 1940.

Bertha reports a case of a glioma in which a large hemorrhage took place. The vascular changes in and around the tumor were studied by the benzidine stain. The tumor, which was a glioblastoma (glioblastoma microcellulare of Gagel), was the size of a fist and lay in the posterior part of the right cerebral hemisphere. There was a large hemorrhage in the tumor, and at its periphery were many polymorphous vessels which in size and shape differed definitely from the normal blood vessels of the brain. These vessels were found in areas without tumor cells. Nearer the tumor a band of proliferated capillary vessels were seen. These vessels could often be followed and were found to arise from one larger vessel. They were very tortuous and were formed like clusters of angioblastic tissue. Similar proliferations of vessels were found deep in the tumor, even in areas away from extravasated blood. They were composed only of an endothelial lining and were surrounded by rich collagenous tissue, which was often hyalinized. The author believes that while much of this vascular proliferation is a reaction to the bleeding, there is sufficient anatomic evidence to postulate independent blastomatous tendencies in the mesenchymal tissue. The term angioblastic glioma is therefore justified. It is conceivable that even mild trauma to the head could cause a hemorrhage from these vessels in the tumor.

SAVITSKY, New York.

Meninges and Blood Vessels

ENCEPHALOMENINGITIS IN MUMPS. M. J. FOX, Wisconsin M. J. **40**:113 (Feb.) 1941.

Fox discusses 4 cases of encephalitis and meningitis complicating mumps. He believes that both conditions are best covered by the term "mumps encephalomeningitis." Clinically the syndrome resembles meningitis rather than predominant encephalitis. Four of the author's patients had some degree of swelling of the parotid glands during the course of the illness. Two patients manifested the neurologic complication by convulsions; 3 complained of headache, 3 of gastroenteritis, especially with vomiting, and all had nuchal rigidity. Spinal puncture disclosed increased intracranial pressure, and all 4 patients had hyperlymphocytosis. The cell counts ranged from 775 to 1,440 per cubic millimeter of fluid. The sugar content of the spinal fluid of the 3 patients tested was below normal. Three patients were extremely ill when admitted to the hospital; all made uneventful recoveries, and up to the present writing no sequelae have been reported. The etiologic agent of the encephalomeningitis associated with mumps appears to be the virus of mumps, as shown by the virulence of the Lavergne test. The neurologic changes of the 4 patients were distinctive of meningitis, and the uniformity of the symptoms seems characteristic. The prognosis of the encephalomeningitis of mumps is more favorable than that of the encephalitis of other communicable diseases.

J. A. M. A.

INTRACRANIAL ANEURYSM. HUGO KRAYENBÜHL, Schweiz. Arch. f. Neurol. u. Psychiat. **47**:155, 1941.

This contribution is based on a comprehensive review of the literature and the author's experience in 32 cases of intracranial aneurysm of the saccular type. In a group of 11 cases in which the diagnosis was confirmed either by arteriographic examination with a colloidal suspension of thorium dioxide or by surgical exploration all the patients were alive. Their ages at the time of observation varied from 12 to 50 years. In 2 cases of infraclinoidal aneurysm of the internal carotid artery extracranial ligation of that vessel was done. Both patients were completely relieved of pain, and their ocular palsies were greatly improved. Clinical signs in the first case consisted of paralysis of the external rectus muscle on the affected side with slight exophthalmos and a minimal degree of corneal anesthesia. A large aneurysm was revealed in arteriograms. In the second case there were exophthalmos, atrophy of the optic nerve and almost complete ophthalmoplegia on the affected side with loss of sensation in areas innervated by the first and second divisions of the trigeminal nerve. Although arteriograms showed nothing abnormal aside from posterior displacement of the middle cerebral artery, a large aneurysm was discovered on surgical exploration. Roentgenologic examination in both cases revealed homolateral erosion of the sella turcica and neighboring structures.

In 2 additional cases of infraclinoidal aneurysm of the internal carotid artery, failure of vision was the chief complaint and perimetric study disclosed bitemporal hemianopia. Arteriographic examination gave negative results in both cases, and roentgenologic examination revealed expansion of the sella turcica with atrophy of the dorsum sellae in only 1 of them. In both instances, however, an intrasellar aneurysm was demonstrated on surgical exploration. In 1 of these cases the aneurysm remained in a collapsed state after its contents were aspirated, with resulting improvement of the bitemporal defect in the visual fields. Signs and symptoms of a progressive lesion of the optic chiasm were likewise noted in a case of supraclinoidal aneurysm of the left anterior cerebral artery. Arteriograms revealed a sac of huge dimensions, and eight days after ligation of the left common and internal carotid arteries there was considerable improvement in the right visual field.

Recurring subarachnoid hemorrhage was the indication for arteriographic examination and immediate ligation of the common and internal carotid arteries on the affected side in 2 other cases of supraclinoidal aneurysm. Although in serious condition at the time of operation, both patients recovered. The aneurysm arose from the anterior communicating artery at its junction with the right anterior cerebral artery in the 1 case and from the left anterior cerebral artery in the other. The oculomotor nerve and the first divsion of the trigeminal nerve were involved in the fourth and fifth cases of supraclinoidal aneurysm. In each of the last-mentioned cases the aneurysmal sac, as demonstrated in arteriograms, arose from the internal carotid artery at the origin of the posterior communicating artery. Ligation of the internal carotid artery in the 1 case and of the common and internal carotid arteries in the other was followed by marked improvement. No operative treatment was undertaken in a case of aneurysm of the posterior portion of the left posterior communicating artery with oculomotor palsy and recurring subarachnoid hemorrhage. Injection of a colloidal suspension of thorium dioxide into the left internal carotid artery gave negative arteriographic results, but the aneurysm was finally demonstrated by injection of the contrast medium into the right vertebral artery according to the method of Moniz. Moniz' method consists in injecting the medium into the subclavian artery after the vessel has been exposed and its distal end occluded.

In the eleventh case, that of a boy aged 15, hemiplegia had developed suddenly on the right side ten months previously, and the patient subsequently had jacksonian seizures. Arteriographic examination revealed dilatation of the left internal carotid artery at the level of the cavernous sinus but failed to show the left middle cerebral artery. A presumptive diagnosis of thrombosis of the left middle cerebral

artery was confirmed on surgical exploration, which, in addition, disclosed a large thrombosed aneurysm of the same vessel. The aneurysm, which was of the congenital type, lay in the white matter of the left frontal lobe and was removed.

In the series of 7,452 autopsies studied, ruptured intracranial aneurysm was found to be the cause of death in 21 cases. The patients' ages ranged from 6 to 78 years. The sites of aneurysm were as follows: anterior cerebral artery, 6 cases; anterior communicating artery, 4 cases; middle cerebral artery, 4 cases; internal carotid artery, 4 cases; basilar artery, 2 cases, and a cerebellar artery, 1 case. Formation of aneurysm was due to arteriosclerosis in 2 cases, focal arteritis in 4 cases and arteritis of embolic origin (mycotic aneurysm) in 1 case. In 6 cases the ruptured aneurysm was of the congenital type, and in the remaining 8 cases the type was not stated. Of 20 cases in which a clinical history was available, the onset of symptoms was abrupt in 16 and gradual in 4. In 1 of the cases of aneurysm of the anterior communicating artery homonymous hemianopia was present. In only 1 of the 7,452 autopsies was note made of an intracranial aneurysm which had been obliterated by thrombosis and subsequent fibrosis.

Clinically, intracranial aneurysms are divided into the paralytic and the apoplectic types. Aneurysm of the internal carotid artery in its course through the cavernous sinus gives rise to a characteristic syndrome consisting of pain and sensory loss in the area of distribution of the fifth cranial nerve and ocular palsies, oculomotor palsy being the most important. All three divisions of the trigeminal nerve are, in general, involved only when the aneurysm lies in the posterior portion of the cavernous sinus; involvement of the first and second divisions is characteristic of an aneurysm in the middle portion of the sinus, whereas involvement of the ophthalmic division alone suggests a more anterior location. The author's first 2 cases were somewhat unusual in that symptoms characteristic of the cavernous sinus syndrome came on gradually, rather than abruptly. The symptoms and signs of an intrasellar aneurysm may differ little from those due to an intrasellar neoplasm. Focal symptoms are much less frequent in cases of aneurysm of the anterior cerebral or the anterior communicating artery. Aneurysm of either the internal carotid or the posterior communicating artery at or near the junction of the two arteries is productive of a well defined clinical picture, consisting of oculomotor palsy and homolateral headache with pain in either the eye or the forehead. Aneurysm of the posterior cerebral artery at the origin of the posterior communicating artery is relatively rare. The symptoms of aneurysm of the middle cerebral artery are not especially characteristic. Bilateral involvement of the sixth cranial nerve when associated with subarachnoid hemorrhage is strongly suggestive of aneurysm of the basilar artery.

Two cases illustrative of the value of cerebral arteriography in differential diagnosis are reported. One was a case of arteriovenous aneurysm with recurring subarachnoid hemorrhage, while the other was one of cerebral glioma with an apoplectiform onset. Valuable though cerebral arteriography is in the diagnosis of intracranial aneurysm, it furnishes no information as to the possible risk of carotid ligation. In none of the author's cases was the contrast medium demonstrated in the opposite half of the circle of Willis, not even when it was injected into one internal carotid artery after the other had been ligated. Although manual compression of the carotid artery for periods of fifteen to twenty minutes on several successive days is a helpful test, it furnishes no positive assurance that the effects of carotid ligation will not be disastrous. In a few of Krayenbühl's cases severe homolateral headache persisted a few days after the procedure, and in 1 case Babinski's reflex could be demonstrated for a time on the opposite side. In 1 of 2 cases of arteriovenous aneurysm, carotid ligation was followed by hemiplegia and aphasia, both of which receded later. Contrary to a view previously expressed, Krayenbühl's experience would indicate that ligation of the internal carotid artery is beneficial even in cases of aneurysm lying distal to the circle of Willis.

DANIELS, Denver.

Diseases of the Brain

INFECTIOUS MONONUCLEOSIS, WITH SPECIAL REFERENCE TO CEREBRAL COMPLICATION. H. E. THELANDER and E. B. SHAW, Am. J. Dis. Child. **61**:1131 (June) 1941.

Thelander and Shaw report the clinical data in 6 cases of infectious mononucleosis, in 3 cases of a postmeasles disorder occurring in triplets and in 3 cases of their own with involvement of the central nervous system presumably a result of mononucleosis. They consider the disease contagious but its communicability low. It produces no immunity. The age incidence cannot be stated accurately. The youngest patient of the author series was 4 years of age, although it is possible that another had the disease when 2½ years old. Persons of both sexes are susceptible to the disease. The symptoms are fever, anorexia, malaise, swollen glands, sore throat and headache; the spleen is enlarged. A few patients have a rash, but this symptom is somewhat variable. The blood picture is sometimes confused with that of lymphatic leukemia. Heterophile agglutination tests serve as a fairly positive diagnostic criterion. According to the authors, no complete pathologic studies have been made in any case of infectious mononucleosis. Biopsy of the glands shows lymphoid hyperplasia which is not diagnostic. There is no specific treatment other than adequate rest and symptomatic therapy as indicated. For some patients with prolonged malaise and fatigability, much rest and supportive treatment over long periods are necessary. The prognosis is said to be good. The authors suggest that some cases of obscure encephalitis may actually be instances of a type of mononucleosis.

WAGGONER, Ann Arbor, Mich.

CHORDOMA OF THE BASIOCCIPUT AND BASISPHENOID. EDWIN BOLDREY and W. J. MCNALLY, Arch. Otolaryng. **33**:391 (March) 1941.

Before 1935 cranial chordoma was considered a rare tumor. Up to the present 85 cases have been reported, to which Boldrey and McNally add 4 of their own. Stained smears are of great value in making the diagnosis. In most cases of chordoma of the basiocciput and basisphenoid the growth is predominantly within the cranial cavity, but in one fifth of the cases it appears in the nasopharynx.

Case 1 was that of a man aged 26 who complained of failing hearing and vision and had signs of involvement of basal structures of the brain, including the second, fifth, sixth, seventh, ninth, tenth and twelfth cranial nerves. Roentgenograms showed erosion of the clinoid processes and the sella. Operation revealed a tumor of the cerebropontile angle. At autopsy a whitish pink, opaque cheesy tumor covering the basiocciput and basisphenoid was found. Sections revealed large cells, occasionally multinucleated, with many nuclear inclusion bodies and many vacuoles in the granular cytoplasm. Connective tissue, intercellular matrix and blood vessels were absent.

Case 2 was that of a man aged 21 with deep occipital pain on the left side, vertigo and a heavy feeling in the upper part of the left side of the jaw. There were slight edema of the left optic nerve and fine lateral nystagmus. Operation revealed tapioca-like neoplastic nodules between the fifth and the seventh cranial nerve on the right side. Autopsy disclosed a yellowish rubbery nodular tumor at the junction of the basiocciput and the basisphenoid. In this case the cells were arranged in definite groups with intercellular substance suggestive of cartilage. A thin plate of bone separated the tumor from the mucous membrane of the sphenoid sinus.

Case 3 was that of a woman aged 50 who complained of severe headache, double vision and tinnitus in both ears. She showed involvement of the right third, seventh, eighth and twelfth cranial nerves. A mass in the epipharynx was firm, more fibrous than cystic, and tough when grasped with forceps. A roentgenogram showed destruction of the basiocciput and basisphenoid at the right petrous apex. A punch biopsy specimen contained no tumor tissue. A specimen obtained by

aspiration showed blood and fragments of friable gray gelatinoid tissue. The smears showed characteristic tumor cells arranged in rows.

Case 4 was that of a girl aged 16 who had transitory weakness of the right lateral rectus muscle four years before admission, with recurrence two years before admission and gradual loss of hearing and vision. On admission there was complete loss of function of the second, fourth, sixth and seventh cranial nerves bilaterally. The third, eighth, ninth, tenth, eleventh and twelfth nerves appeared to be partially involved. Roentgenograms showed a tumor of the sella with erosion of both petrous pyramids. A mass could be seen in the nasopharynx. Part of it was firm and part fluctuating.

Erosion of bone was not noted in the roentgenograms in any of these cases. Pneumographic visualization was a major factor in determining operation. Final diagnosis was possible only by microscopic examination. A nasopharyngeal mass must be regarded as possibly sarcoma, fibroma or chordoma. Smear preparations are of greater value in diagnosis than cut sections, although the latter are also necessary for diagnosis. Chordomas grow so slowly that even in the absence of treatment many years elapse before death. Radium and roentgen therapy undoubtedly was of benefit in case 3.

HUNTER, Philadelphia.

EQUINE ENCEPHALOMYELITIS IN MASSACHUSETTS. V. A. GETTING, New England J. Med. **224**:999 (June 12) 1941.

From an analysis of 34 certain cases of equine encephalomyelitis due to the eastern variety of virus that occurred in southeastern Massachusetts during an epidemic of the disease in horses, Getting observed permanent sequelae (mental retardation, hemiparesis, aphasia and emotional instability) in 6 of the 9 surviving patients. Approximately 70 per cent of the patients were infants and children less than 10 years of age. The 9 surviving patients, in whose blood neutralizing antibodies to the virus were found, were seen at varying intervals from the date of the original illness. It is impossible to prognosticate the eventual course of the residual sequelae. It seems that they are permanent, and may even be progressive. As soon as the true nature of the equine encephalomyelitis outbreak was realized, a mosquito survey was undertaken. In all, 56 different species of mosquitoes were collected, and of them 37 were of the biting kind. Only 6 of the biting species have been shown experimentally to transmit the eastern virus of equine encephalomyelitis to laboratory animals. There were 3 salt marsh species—Aedes cantator, Aedes sollicitans and Aedes taeniorchynchus—anl 3 fresh water species—Aedes atropalpus, Aedes triseriatus and Aedes vexans. The former are usually limited to within 10 miles (16 kilometers) of salt water. Two of the fresh water vectors, Aedes triseriatus and Aedes vexans, were statewide, the latter being from five to fifteen times as prevalent as the former. Aedes vexans is probably the most important vector of equine encephalomyelitis in Massachusetts. The epidemiologic and entomologic data support the laboratory evidence that equine encephalomyelitis is transmitted by mosquitoes, since the geographic distribution and the seasonal prevalence of the disease and the vectors have been found to be the same. The biting habits of the vectors suggest that the hazard of exposure of men and animals to the mosquitoes is ten times as great outdoors as it is in buildings. Thus the high incidence among the young may be explained, as during the summer infants and children often sleep outdoors, sometimes without protective netting. Moreover, children less than 10 years of age who play outdoors the greater part of the day are less efficient than older groups in protecting themselves against mosquitoes, since they do not react to the buzzing and alighting of a mosquito but notice only when bitten. Of the mosquitoes captured on man outdoors, 60 per cent were vectors, as compared with only 6 per cent of those caught indoors.

J. A. M. A.

Diseases of the Spinal Cord

PNEUMOPERITONEUM SUPPLEMENTING PHRENIC PARALYSIS. A. B. RILANCE and F. C. WARRING JR., Am. Rev. Tuberc. **44**:323 (Sept.) 1941.

Rilance and Warring point out that their experience with pneumoperitoneum has been confined to its use as a supplement to phrenic paralysis in an attempt to elevate the paralyzed hemidiaphragm. Indications were those usually accepted for phrenicectomy. Frequently the combined procedure resulted in closure of the cavity and in the sputum's becoming negative when phrenicectomy alone had failed. Supplementary pneumoperitoneum was carried out on 55 consecutive patients with pulmonary tuberculosis treated by phrenicectomy. The patients were observed for from twelve to thirty-five months. In 18, or 33 per cent, an insufficient elevation of the diaphragm (2 cm. or less) was obtained and the use of pneumoperitoneum was discontinued. Of the remaining 37 patients, 1 had minimal, 9 had moderately advanced and 27 had far advanced pulmonary tuberculosis. Only 1 patient had a negative sputum before treatment; 15 of the 36 with a positive sputum later had a consistently negative sputum; 3 have continued to show an intermittently positive sputum (2 of these show definite evidence of tracheobronchial tuberculosis), and the sputum of 18 has remained consistently positive during and after treatment. Definite cavities were evident in the stereoroentgenograms of 34 patients, all with positive sputum, prior to treatment. The rise of the hemidiaphragm after phrenicectomy averaged 3.8 cm. in the 37 mechanically successful instances. The average additional elevation from pneumoperitoneum was 4.1 cm.; the average total rise was 6.9 cm. The cavities of 19 of the 34 patients with open cavities closed after treatment; in 2 they were questionably closed, and in 10 they became smaller. Cavities of various sizes seemed to respond almost equally well. The highest incidence of closure was found among cavities located in the lower third of the pulmonary field, the next highest among cavities in the apex and the lowest among those located in the middle third. J. A. M. A.

INTRAMEDULLARY EPIDERMOID CYST OF THE SPINAL CORD. MURRAY A. FALCONER and REGINALD S. HOOPER, Brit. J. Surg. **28**:538 (April) 1941.

Falconer and Hooper report a case of epidermoid cyst of the spinal cord occurring opposite the second and third thoracic vertebrae. Clinically, the patient had loss of abdominal reflexes on the left side and slight wasting, weakness and spasticity of the left leg. No sensory disturbance was demonstrable. Lumbar puncture showed a partial manometric block, with no increase in the protein content.

At operation the intramedullary cystic mass was successfully removed.

STUCK, Denver.

THE DUMB-BELL TUMOURS OF THE SPINE. KENNETH EDEN, Brit. J. Surg. **28**:549 (April) 1941.

Eden found 32 dumbbell tumors in a series of 234 tumors of the spine. Twenty-five of these were solitary or multiple neurofibromas, 3 were meningiomas, 2 were hemangioendotheliomas, 1 was a ganglioneuroma and 1 was an endothelial cell sarcoma.

The dumbbell shape is caused by a number of factors, depending on the location and the pathologic nature of the tumor. The dumbbell meningioma is confined to the intradural and extradural types and is produced by direct infiltration of the dura. All types of dumbbell neurofibroma may be formed, depending on the portion of the spinal root from which the tumor arises; for example, an extradural and paravertebral tumor is formed when the site of origin is the segment of the

nerve which passes through the foramen. Less commonly, a primary extradural tumor worms its way out of the spinal canal through one or more foramens or between two eroded laminas, to form a secondary extraspinal lobe. The dumbbell ganglioneuroma is formed as the result of a disorder of a segment of the developing sympathetic system, during its migration from the ganglionic crest.

There are two main clinical types of dumbbell tumors, that in which the syndrome is one of compression of the spinal cord with or without a paravertebral tumor and that in which a paravertebral tumor is detected but no signs of paralysis are present.

In addition, the recurrence of paralysis at the same level after the removal of a spinal neurofibroma and the onset of spinal compression following the excision of a paravertebral tumor are both suggestive of the presence of a dumbbell tumor which has been overlooked.

Roentgenographic examination provides valuable evidence of the nature and position of these tumors in the form of enlargement of foramens, paravertebral opacities and occasional gross erosion of the vertebral bodies, with collapse and scoliosis.

Although in cases of neurofibromatosis scoliosis may be associated with multiple dumbbell tumors of the spine, the characteristic spinal deformity of the disease is a separate and distinct condition.

In the presence of compression of the spinal cord, a dumbbell tumor should be approached first by laminectomy, in order that the paralysis may be relieved. If the tumor cannot be excised in one sitting through an extension of this operation, the paravertebral portion can be left behind, to be dealt with directly later.

STUCK, Denver.

ACUTE ANTERIOR POLIOMYELITIS AND VITAMIN B DEFICIENCY. K. HELMS, M. J. Australia **1**:717 (June 14) 1941.

Helms expresses the view, based on a review of the extensive literature, that vitamin B deficiency is a predisposing cause of acute anterior poliomyelitis. He finds indirect evidence in the fact that poliomyelitis tends to occur with greater frequency when the demands for vitamin B_1 (thiamine) are heavy, as in childhood, pregnancy, in substandard nutritional states and after excessive muscular exercise in children or young adults. There are points of resemblance, too, between poliomyelitis and beriberi, which is known to be caused by vitamin B_1 impairment. The direct evidence, the author thinks, would be supplied if suitable tests could be devised. He suggests the investigation of the vitamin nutrition of patients suffering from poliomyelitis. These investigations should include the intake of the vitamin B complex, the conditions which increase the need for the vitamin or interfere with its absorption and, in adults, the amount of alcohol and narcotics taken. The presence of neutralizing substances in the blood may tend to reduce the occurrence of the paralytic form of the disease but does not seem to be a potent factor. The low incidence of paralytic poliomyelitis among those exposed to the disease may be due to the fact that this form occurs only when the biochemical state of the central nervous system favors the propagation of the virus. Vitamin B deficiency may constitute one cause of biochemical alteration. One investigator, reporting 5 cases of acute poliomyelitis, attributed the rapid recovery, with freedom from paralysis or rapid regression therefrom, to vitamin B therapy. Ordinary white flour, made from grain milled according to modern processes, consists entirely of starchy endosperm and contains neither the germ nor the bran, the former of which is nutritionally the best part of the seed. It is poorer than whole meal flour in vitamin B_1 (thiamine) and vitamine B_2 (riboflavin), both of which are concerned with tissue respiration. Modern milling processes were adopted in 1870. Acute anterior poliomyelitis seems to have increased since 1880. J. A. M. A.

Treatment, Neurosurgery

INDUCED HYPOGLYCEMIA IN THE MANAGEMENT OF OPIATE WITHDRAWAL. S. J. TILLIM, Psychiatric Quart. **15**:460 (July) 1941.

Tillim reports 7 cases in which addiction to morphine and diacetylmorphine was treated with insulin and adjuvants. The general technic consists in rapid withdrawal of the opiate. When withdrawal symptoms appear, insulin is administered, the dose being estimated by trial. Objectives for estimation of the dose are relaxation, sleep, diaphoresis and hunger in two to three hours. Deep stupor and coma should be avoided and may be interrupted by intravenous injection of dextrose. After acute symptoms subside the dose of insulin is reduced. When all signs of withdrawal disappear the treatment is discontinued. Symptomatic adjuvants used were warm baths, massage, metrazol and amphetamine (benzedrine) sulfate. Sedatives are avoided as much as possible. In most cases seven to nine days of treatment are sufficient. The results reported appear to be favorable.

SIMON, Middletown, Conn.

ELECTRIC SHOCK THERAPY IN THE PSYCHOSES: CONVULSIVE AND SUBCONVULSIVE METHODS. S. ANDROP, Psychiatric Quart. **15**:730 (Oct.) 1941.

Androp reports on the results in 50 cases of psychoses of moderate chronicity (duration one to fifteen years, with an average of four years), in which 1,004 shocks were given. One third of the patients had convulsions and two-thirds subconvulsions. Fifty-two per cent improved in some degree, the greater incidence of improvement (60 per cent) occurring with convulsive doses. With subconvulsive doses there was less response (46 per cent). Relapses within a year amounted to 15 per cent. Those who received subconvulsive doses were twice as likely to relapse. The duration of the illness was inversely related to the response. The rate of improvement among nontreated patients was 33 per cent during the first year of hospitalization. Intensive psychotherapy is reported to have played an important role in the incidence of improvement. Patients with affective disorders and schizophrenic patients with affective display responded best. Induction of shock twice a week seemed more effective than more frequent administration.

The complications were similar to those encountered in metrazol therapy. Fear was less marked, though dislike of the treatment was generally present. The results were considered to compare favorably with those following metrazol. It is suggested that the incidence of relapse may be less, on the basis of a report of 50 per cent relapse after two years in a group of similar patients treated with metrazol.

SIMON, Middletown, Conn.

ARTIFICIAL FEVER THERAPY IN GENERAL PARESIS WITH ELECTROENCEPHALOGRAPHIC STUDIES. A. E. BENNETT, P. T. CASH and C. S. HOEKSTRA, Psychiatric Quart. **15**:750 (Oct.) 1941.

The authors give a general review of the present status of fever therapy for dementia paralytica and report on the results of combined artificial fever and chemotherapy in a series of cases. In a series of 50 patients, most of whom had a mild or intermediate form of the disease, 50 per cent had full remissions and 90 per cent were improved. In one third of the patients with positive reactions of the blood and in two-thirds with positive reactions of the spinal fluid serologic reversals were obtained. Of 79 patients in state hospitals, 50 per cent of whom had a severe form of the disease, one-half improved (of whom 19 per cent had remissions). Serologic reversals were less frequent in this group. In nearly a third of the patients who had had previous malarial therapy a full remission was obtained. Forty-two per cent showed no further improvement. Of 15 patients with previously treated, asymptomatic neurosyphilis, 46.6 per cent responded with serologic reversal of the blood and 73.3 per cent with serologic reversal of the spinal fluid.

In 4 patients with acute early dementia paralytica abnormal alpha waves and slow potentials were evident in the electroencephalogram. Three patients with clinical remission showed marked improvement in the electroencephalograms immediately after treatment. In 8 of 10 patients who failed to have a remission abnormal electroencephalograms persisted one to three years after treatment. In general, the authors consider combined artificial fever and chemotherapy superior to malarial therapy and recommend its use for patients in whom malaria has failed to produce full remission.

SIMON, Middletown, Conn.

MAPHARSEN IN THE TREATMENT OF BENIGN TERTIAN MALARIA. D. WHITEHEAD and J. J. DOREY, Psychiatric Quart. **15**:790 (Oct.) 1941.

Problems inherent in the use of quinine for the eradication of therapeutically induced malaria led the authors to investigate the efficacy of mapharsen. The two major problems, aside from the antipaludal efficiency of quinine, involved lack of cooperation in psychotic patients and toxicity of the drugs. In 7 of 9 patients tertian malaria was eradicated. The remaining 2 patients suffered persistent recurrences. For these patients a combination of quinine and mapharsen was recommended. Mapharsen was found less toxic (arsenic-sensitive patients excluded), quicker and surer in its action than quinine. Its antisyphilitic effect was also stressed.

SIMON, Middletown, Conn.

THE SURGICAL TREATMENT OF SYRINGOMYELIA. C. WORSTER-DROUGHT, CECIL P. G. WAKELEY and J. SHAFAR, Brit. J. Surg. **29**:56 (July) 1941.

As a result of their study of the literature and their own experience in 10 cases of syringomyelia in which operation was performed, the authors conclude that surgical treatment is not indicated in cases of mild or stationary syringomyelia and should be carried out only in those cases in which the disease is obviously progressive, as the natural tendency of this disease is to progress slowly and possibly to be interrupted by periods of quiesence.

They reach no conclusion regarding the cause of this condition but discuss most of the literature on the subject. They believe that in the cases selected for operation there should be definite subarachnoid block and roentgenographic evidence of obstruction when iodized poppyseed oil is injected.

At operation, the authors obliterate the cavity and attempt to produce fibrosis within it, so that the walls may become adherent. This is done by painting the cavity with a weak solution of iodine after opening and draining it. They believe that the most one can accomplish surgically is arrest of the condition.

STUCK, Denver.

Encephalography, Ventriculography, Roentgenography

THE SYNDROME OF INTERNAL FRONTAL HYPEROSTOSIS. NATHAN ROTH, Am. J. Psychiat. **98**:63 (July) 1941.

Roth reports the clinical data on 8 patients with internal hyperostosis frontalis. The patients were all obese females, the obesity being chiefly of the face, neck and trunk. Most of them had hypertension and facial hirsutism. Four had diminution or absence of sexual desire. All but 1 had abnormal dextrose tolerance curves. Four had creatinuria and only 1 hypercalcemia. No significant changes in the spinal fluid were noted. All 8 patients presented psychiatric abnormalities, which Roth concluded were not related to the hyperostosis frontalis. In addition, 1 patient had idiopathic grand mal epilepsy, another migraine and a third herpes zoster in the area supplied by the ophthalmic division of the trigeminal nerve. These states, also, could not be attributed to the disease. Roth is of the opinion that the local physical factors are significant for the deposition of the calcium salt and that large amounts of calcium salt are present in the cerebro-

spinal fluid, owing to increased permeability of the blood-brain barrier. The depositions occur where the curvature of the skull bones is greatest, as the flow of cerebrospinal fluid is likely to be slowest there. The increased permeability of the blood-brain barrier is attributed to hypertension, arteriosclerosis or endocrine factors.

FORSTER, Boston.

PNEUMO-ENCEPHALOGRAPHY IN EPILEPSY. WILLARD W. DICKERSON, Am. J. Psychiat. **98**:102 (July) 1941.

Dickerson studied by means of air encephalograms 286 institutionalized epileptic patients. The encephalographic procedure was strictly standardized and routinized for the entire group. All of the films were interpreted by one person. From a diagnostic viewpoint, the author found that air encephalography could be of little aid in determining the etiologic agent but was of value in the selection of patients for neurosurgical therapy. From a prognostic point of view, it is most valuable in offering confirmation of the obvious neurologic signs. One hundred and twenty-two of Dickerson's patients were followed sufficiently long to arrive at some conclusion to be reached regarding the effect of the procedure on the frequency of the seizures. In 25 of these 122 patients seizures were decreased after the examination, and in 33 they were increased.

FORSTER, Boston.

INTRATHORACIC NEUROGENIC TUMORS. KARL KORNBLUM and HOWARD H. BRADSHAW, Radiology **37**:391 (Oct.) 1941.

Tumors within the chest are often best detected roentgenographically, as they frequently attain large size without giving many signs or symptoms. Detection of such tumors is relatively easy, but to determine the nature of the neoplasm is often extremely difficult. Since treatment and prognosis are dependent on the nature of the lesion, it is of great importance to distinguish one tumor from another, and an analysis of the roentgenogram plus a clinical evaluation of the case will often serve to establish a correct diagnosis.

Tumors occurring within the chest are many and varied, the more common being primary carcinoma of the bronchi and lungs; many varieties of metastatic tumors; lymphoblastoma, such as Hodgkin's disease and lymphosarcoma, and aneurysm of the thoracic aorta. There is also a large variety of less frequently seen tumors, and to this group belong the tumors of neurogenic origin.

The clinical features of these tumors is not specific. There is no age or sex predilection. The onset of symptoms is usually slow but at times may be abrupt, and depends mainly on manifestations of pressure by the tumor mass. As the tumor may occur anywhere in the chest, the location determines the symptoms to a large extent. The majority of such tumors are in the posterior portion of the chest, and here they may attain large size without producing many symptoms. The most common symptoms are pain in the chest and cough; these are rarely absent. Pain is more common with the malignant lesions and may radiate to various structures, particularly to the shoulder on the side of the lesion. Loss of weight is also common, especially in cases of the malignant lesions. Aphonia may occur from involvement of the recurrent laryngeal nerve or dysphagia from implication of the esophagus. Pressure on the mediastinum may result in dyspnea, a sense of pressure beneath the sternum or cyanosis.

Physical signs are usually evident, owing to the large size that the lesion commonly attains. There are flatness to percussion over the tumor and absence of breath sounds. The physical signs are dependent on the location of the tumor and vary from evidences of mediastinal shift due to pressure to evidences of obstruction of a bronchus, with resulting atelectasis.

Even abdominal signs may be produced by large tumors just above the diaphragm causing downward pressure and producing readily palpable liver, spleen or kidneys.

Complications are common. Infection is often seen because of interference with drainage from the lung and the presence of atelectasis. Paralysis of the

phrenic nerve may be encountered. Symptoms of involvement of the spinal cord may occur, but are usually caused by a tumor which originates within the vertebral canal and emerges through the intervertebral foramen, the so-called dumbbell tumor.

The roentgen examination should consist of a careful fluoroscopic and roentgenographic study. The lateral view of the chest should be obtained in every case, as the common posterior position of the tumor is best demonstrated in this exposure. Oblique stereoscopic exposures and roentgenograms made with the Potter-Bucky diaphragm are also of value. Body section roentgenograms may aid in some cases. Films made after induction of artificial pneumothorax are often valuable.

The roentgenographic appearance depends on the presence or absence of complications. In the uncomplicated case there is a dense, homogeneous, well circumscribed, sharply defined, spherical or globular mass, which may be found anywhere in the chest but is most commonly seen posteriorly. Neighboring structures, such as the heart, the mediastinum, the trachea, the esophagus or the diaphragm, may be displaced, depending on the size and location of the tumor.

In cases with complications the ordinary features may be lost or masked, so that the nature of the tumor is not recognized. Atelectasis or pleural effusion may change the picture markedly, and secondary infection may cause the entire mass to be considered as inflammatory.

Many lesions must be differentiated. The lymphoblastomas (Hodgkin's disease and lymphosarcoma) are confined to the mediastinum, are usually nodular and often have glandular enlargements elsewhere. These tumors respond readily to irradiation, while the neurogenic tumor is highly radioresistant. Lymphatic leukemia is rarely manifested by an isolated tumor in the mediastinum and gives the blood picture characteristic of the disease. An aneurysm may be difficult to differentiate, as it may closely resemble a neurogenic tumor. It can usually be noted to arise from the aorta. The Wassermann reaction may aid in diagnosis. Dermoid cyst produces the same type of shadow as does the neurogenic tumor but is usually anterior, in contrast to the common posterior position of the neurogenic tumor. Thymoma is likewise located anteriorly and is usually irregular in contour. Large, single, isolated metastatic lesions, such as result from hypernephroma or teratoma of the testis, may be difficult to differentiate, as are intrathoracic fibroma and lipoma.

The only treatment of any avail is surgical removal of the tumor. Roentgen irradiation is of no value.

In the last four years, the authors have seen 7 tumors of this type, including 2 neurofibromas, removed surgically with excellent results, 1 neurofibroma, with sudden death following peritoneoscopy, and 3 malignant neurogenic tumors. No evidence of metastasis was found in any case.

Good results may be obtained by surgical treatment in cases of the benign lesions, regardless of their size. The question of malignancy can usually not be determined roentgenographically, but invasion of the lung at operation is indicative of malignancy. The tumor is probably more common than is supposed, and a dense, rounded, well circumscribed shadow in the posterior portion of the chest should suggest its presence. A mass in the posterior part of the mediastinum associated with symptoms of involvement of the cord is probably a neurogenic tumor. Careful and adequate roentgen study is the most important single means of their detection. Helpful in the detection are diagnostic pneumothorax, bronchoscopy and aspiration or punch biopsy.

KENNEDY, Philadelphia.

LEONTIASIS OSSEA. GEORGE K. KIRKLAND, Brit. J. Surg. **29**:74 (July) 1941.

Leontiasis ossea usually begins insidiously, often in late childhood or adolescence. The skull gradually increases in size, and usually one or more areas of localized increase appear, particularly in the frontal region, giving the appearance of bulging of the forehead. Headache usually commences at an early stage in the

disease, sometimes before the deformity is noticed. The pain is usually paroxysmal but may be constant. Nasal obstruction and interference with chewing are often early symptoms and may be serious. Ocular symptoms are dangerous; there may be exophthalmos, proptosis, epiphora and atrophy of the optic nerve. In extreme cases the eye may be so exposed that corneal ulcer and traumatic rupture of the globe occur. Pressure on the nerves emerging from the skull may result in neuralgia or facial paralysis. Interference with the circulation may arise, and dilated superficial veins may be present, indicating the establishment of a collateral circulation. Stenosis of the carotid artery is said to give rise to a rushing sound in the ear, which can be controlled temporarily by pressure over the artery. Insomnia is usually present. There is sometimes an inverted sleep rhythm suggestive of pituitary trouble, although no other symptoms of involvement of the pituitary have been recorded. Patients with the disease are said to be apathetic, but this conclusion or opinion is due probably to the fact that facial expression is practically lost in the advanced stages. Convulsions are usually a late phase, and paralysis of the limbs has been seen in the terminal stages. The condition is progressive and is said to be fatal in twenty to thirty years. STUCK, Denver.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

HARRY PASKIND, M.D., *President, in the Chair*

Regular Meeting, April 17, 1941

Present Status of Myasthenia Gravis. DR. HENRY R. VIETS, Boston.

My associates and I have made an extensive study of myasthenia gravis at the Massachusetts General Hospital since 1934 and from that date through April 1941 have made a diagnosis in 84 cases of this disease. This is a large number as compared with any previously reported series. The records of the hospital show that for the thirty year period prior to 1935 the diagnosis was made only about once a year. The discovery in 1934 that prostigmine was an effective, although palliative, type of treatment led to a reevaluation of the whole problem of myasthenia gravis. A special clinic was established in 1935, and patients began to come in from Boston, and indeed from all New England and other parts of the United States.

The disease has been studied from many points of view, on the assumption that in myasthenia gravis there is a defect in the transmission at the myoneural junction of the nerve impulse to the muscle. It has been established that at this junction, known as the synapse, acetylcholine is secreted at the time of the passage of the impulse and that the amount of acetylcholine or the length of time that it is available is controlled by a destructive chemical substance, cholesterase. Thus it would appear that, whatever the nature of the impulse, whether electrical or otherwise, the maintenance of a chemical state at the synapse based on a balance between the amount of acetylcholine and the cholesterase is necessary. In myasthenia gravis the balance between these two chemical substances is upset, leading to a state of unusual fatigue, with recovery after rest, as the principal clinical symptom. In one sense of the word this fatigue is only an exaggeration of a normal physiologic state, for fatigue and recovery are the natural constituents of a healthy body state. There are other factors in myasthenia gravis, however, such as the progress of the disease by remissions and relapses, the selectivity of the disease in relation to certain muscle groups, the varying ages of the patients, the degree of involvement in certain age groups, the fatality of the disease in spite of adequate treatment, especially in females in the third decade of life, the occasional association of the disease with hypertrophy of the thymus gland and the remarkable effects of pregnancy on the clinical course.

With these factors in mind, certain clinicophysiologic studies have been carried out. A test for the disease was developed based on the response to injections of prostigmine methylsulfate, with a method of scoring and recording the results. An ampule of prostigmine methylsulfate and atropine containing the proper dose for the prostigmine test has recently been made available. This test has proved highly satisfactory in making the diagnosis of the disease, for in no patient with any condition other than myasthenia gravis has the reaction been positive. If a patient is free from the effects of prostigmine, the diagnostic test has proved in our hands to be efficient.

A more exact diagnostic test than simply the observed increase in muscular response or the subjective report from the patient after the injection is the effect on the ergogram or the electromyogram. With these two tests results can be obtained that are unmistakably characteristic of myasthenia gravis. This is also true, at least in large part, in the fluoroscopic examination of the swallowing reflexes with the aid of barium sulfate before and after injection of postigmine

methylsulfate. This new modification of the prostigmine test has recently proved of value in patients suffering from various forms of dysphagia. Other tests have been used, but none has proved to be of value. Cystometric examination of the bladder, a study of the cerebrospinal fluid and the electroencephalographic and electrocardiographic procedures all give results within normal limits in cases of myasthenia gravis.

A system of treatment based on the use of prostigmine bromide by mouth has been evolved. Rarely is it necessary to administer the drug by injection, and this form of treatment is reserved for the patient having severe respiratory embarrassment. All patients taking prostigmine by mouth, however, are advised to have at hand ampules of prostigmine methylsulfate for use in case of emergency. The oral treatment is given by a schedule that is set throughout the hours of the day, and even during the night. The majority of the patients take prostigmine bromide every two or three hours during the day, the average maintenance dose being 6 or 8 tablets of 15 mg. each. Some patients take two, or even three times this amount, and the intake by day may be augmented by some medication at night. Rarely is it necessary to take at one time more than 2 tablets of 15 mg. each. A few patients take 3, but the symptoms caused by this large amount of prostigmine are often unpleasant, and for a normal person would be indeed serious. One is impressed, however, by the fact that a patient with myasthenia gravis can take large amounts of prostigmine bromide by mouth, as well as certain other drugs, without having any untoward symptoms. One of the patients has been maintained on as many as 20 to 25 tablets (15 mg.) a day for well over a year.

In addition to prostigmine bromide by mouth, with occasional use of prostigmine methylsulfate by intravenous injection, three other drugs have been found helpful as adjuvants to this therapy. Ephedrine sulfate is the most useful, and indeed was used by itself for a number of years before the more efficient prostigmine bromide was discovered. Guanidine hydrochloride is also somewhat useful, not in our hands by itself, but as an adjuvant to prostigmine. Potassium salts, on the other hand, are useful by themselves if they can be taken in large enough doses to be effective. This is not by any means easy, as large oral doses are difficult to take. As a method of adding to the effectiveness of prostigmine bromide in maintaining reasonably good health, the potassium salts, guanidine and ephedrine are all important. Another drug, congo red, is effective, but cannot be used clinically.

A large number of other drugs have been tried in the clinic in the last six years, some of them being slightly effective, but most of them ineffective. These include caffeine citrate, digitalis, aminoacetic acid, amphetamine sulfate, thiamine hydrochloride. A number of endocrine preparations have also been used. These substances, including testosterone propionate, estradiol dipropionate, progesterone, desoxycorticosterone acetate, chorionic gonadotropin (antophysin) and thymus extract, have all been noneffective.

The results from time to time are checked by a statistical method, the subjective symptoms and general appearance of the patient and the effect on any special symptom, the ergogram and the electromyogram being noted. We feel that the results are fairly satisfactory if we are able to keep the patient's efficiency above 75 per cent of normal, and this we have been able to do in a majority of the cases.

Pregnancy usually has a marked effect on the disease. Of 5 patients who have been pregnant while under observation, 2 of them on two occasions, all but 1 have shown complete remission of all symptoms during the course of the pregnancy. The onset has begun as early as the second or third week of pregnancy, but in most cases symptoms begin to disappear in the second or third month. The remissions have been more prompt, and in most cases more extensive, than one would expect in the ordinary course of the disease. Relapses occur after delivery, but in no case has the relapse occurred so suddenly or so severely that the situation could not be controlled by prostigmine, either by injection or by mouth.

The relation between prostigmine and myasthenia gravis is not clear at present. Neither is the relation, if any, between this disease and hypertrophy of the thymus gland. In our series of cases we have never been able to demonstrate enlargement of the gland roentgenographically. In spite of this, however, on the basis of the experiences of others, we have treated a number of patients with roentgen therapy, although the results of such treatment have not been striking.

In general, we can report that the results of continued observation on and treatment of our 84 patients during the last six years have led to a situation which is much more satisfactory than has ever been obtained before in this disease. Fifty-four of the patients are able to work; 12 of them have had complete remissions, 10 have had partial remissions, and there have been only 13 deaths.

Myasthenia gravis is still a puzzle, wrapped in mystery. Involved with it is an enigma, the mechanism of neuromuscular transmission. We have unwrapped a little of the mystery and see the puzzle more clearly than we did five or six years ago. The key to the enigma still evades us.

DISCUSSION

DR. R. P. MACKAY: Has Dr. Viets, in his experience with this disease, obtained any evidence that it may be hereditary? On one or two occasions pregnant women have wished to know whether their children might inherit their condition. Will Dr. Viets also comment on the reason for his use of atropine with prostigmine and on the antagonism between prostigmine and quinine?

DR. ROY GRINKER: The two points brought up in regard to pregnancy and tumors of the thymus are interesting. I was asked in 1931 by a patient with myasthenia gravis whether she should become pregnant. I advised against it, but she became pregnant anyway, and made a complete recovery during the time she was pregnant. After delivery she was much improved and was able to get along fairly well until later, when prostigmine was available. She is now using this drug, with benefit.

The question of tumors of the thymus is extremely interesting. My associates and I have had 2 cases. In 1, from the clinic, the roentgenogram showed a tumor and high voltage roentgen therapy helped a great deal. In the other, in which prostigmine was also of help for some time, a tumor proved at autopsy to be malignant.

DR. HENRY R. VIETS, Boston: These questions illustrate what I have been saying, that not much is known about the disease. I am asking myself these same questions all the time. I have not felt justified in operating on any patients, for in our series the thymus gland has not appeared in the roentgenograms. I have seen nothing to indicate a hereditary tendency. I have not encountered 2 cases in one family and have not had any history of such an occurrence.

Atropine is used at the beginning of the treatment to overcome increase in peristalsis, which occurs with prostigmine therapy. I think there is no danger in the diagnostic ampule which has atropine in it. At first most patients take tincture of belladonna or atropine, but after a week or two they discontinue it. Even when our patients are taking as high as 20 to 25 tablets of prostigmine bromide of 15 mg. each, which is enough to affect seriously any normal person, they do not need atropine after a few days or weeks. A certain tolerance is acquired to its use. Quinine is dangerous. It makes the myasthenia worse.

I do not understand why these remarkable remissions occur during pregnancy. They may take place rapidly. For instance, one patient, who was taking 12 tablets a day for six or eight months, began to be better even before she missed her first period. In other words, she made the diagnosis of presumptive pregnancy very early in the pregnancy. If acetylcholine is formed by the placenta, one could not conceive of its being formed in sufficient amounts in ten days. Most patients do not begin to show the effect until after eight weeks or so.

Malignant tumors of the mediastinum have been reported as affecting patients with myasthenia gravis. That ties up with the theory of the role of the thymus

gland. We obtained Dr. Rowntree's thymus extract and injected it in 3 patients with myasthenia gravis, without effect.

The tolerance to prostigmine is interesting. Many patients can take an extraordinary amount. A physician in New Haven took 3 tablets of the bromide (15 mg. each), with severe symptoms. One of our patients, however, has taken 20 to 25 tablets a day for three years and has not the slightest symptom of trouble from the drug itself. When we have patients who do not tolerate large doses of prostigmine well, we discontinue the drug for twenty-four hours and substitute potassium. They then go back to prostigmine on a smaller dose. There is a slight intolerance to it occasionally, but that is not an important factor in our cases. There is no hazard in its use, either diagnostically or clinically, with ordinary care.

Action of Pyridine and Some of Its Derivatives in Preventing Convulsions Produced by Metrazol. Dr. L. J. Pollock and Dr. I. Finkelman.

Review of the Symptomatology of Alzheimer's Disease. Dr. Alfred Paul Bay and Dr. Jack Weinberg.

DISCUSSION

Dr. Arthur Weil: This case has been well presented, and there can be no doubt about the correctness of the diagnosis. The unanswered question in cases of Alzheimer's disease is that of the cause. In this case there was a concomitant mild degree of arteriosclerosis, but one cannot consider this as a determining factor in producing the marked atrophy of the brain. Von Braunmuhl expressed the concept of physicochemical changes in the brain, a hysteresis, which leads to disintegration and argyrophilia. Others have assumed the presence of "endotoxic" factors, without presenting any more conclusive evidence than that supporting the hypothesis of vascular disturbance. The presence of chronic hepatitis in this case might give some comfort to those adhering to the first hypothesis.

Dr. George B. Hassin: The plaques, or drusen, so beautifully demonstrated by Dr. Bay are not considered typical of Alzheimer's disease. Their presence merely renders one suspicious that the brain may be senile, though they have been found in brains of elderly, mentally healthy people. Nor are the areas of devastation (*Verödungsbezirke*) of importance. What is considered pathologic in Alzheimer's disease are the changes in the ganglion cells, among them Alzheimer's neurofibrils. I wonder whether Dr. Mackay saw in this brain the neurofibrillary changes in the ganglion cells described by Alzheimer.

Dr. R. P. Mackay: Histologically, the intracellular changes of Alzheimer's disease were pronounced in this brain. They could be seen in the slides demonstrated by Dr. Bay, but were not obvious because of the low magnification.

I am not convinced whether Alzheimer's disease is truly a disease or not. As Dr. Hassin pointed out, the plaques occur in other conditions and are not characteristic. However, those relatively young persons who show premature senile changes clinically and whose brains present the combination of the argentophilic plaques and the intracellular changes form a striking and somewhat characteristic group. All these features combined suggest that something rather specific is going on behind the scenes.

Dr. Herman Serota: The electroencephalogram in this case which my colleagues and I took at Michael Reese Hospital was unusual, and I should like to show it. There was little activity from the frontal pole except for large, smooth changes in potential, and the activity obtained from the occipital pole was rather irregular. The only occasion on which we have seen tracings similar to those of the frontal pole is when electrodes are moved about very slowly in a disk of saline solution or spinal fluid. Attempts were made to rule out artefacts. In view of the microscopic changes and the electroencephalogram, it is possible that the amount of histologic atrophy may not be indicative of how much actual dysfunction existed in that particular area.

DR. JACK WEINBERG: In reviewing the literature (altogether less than 100 cases were reported), one finds a number of theories as to the cause of the pathologic changes, but certainly there is no unanimity on the subject. McMenenery pointed out that in all cases in which Alzheimer's disease is suspected or confirmed a thorough investigation into the pathologic changes in other organs should be made and the changes correlated for an evaluation of possible etiologic factors. At present, in the Chicago State Hospital we have a number of patients whose condition has been classified with the involutional psychoses but whose symptoms and progress lead us to believe that the disorder falls under the so-called presenile psychoses. We are reexamining these patients in the light of present knowledge and with the aid of newer diagnostic methods, hoping to isolate them and possibly to make a clinical diagnosis in some cases, before a necropsy is performed.

Dr. Hassin is quite right. The neurofibrillary changes, not so much the senile plaques, constitute the outstanding feature of Alzheimer's disease.

ROY R. GRINKER, M.D., *President, in the Chair*

Regular Meeting, Oct. 16, 1941

Surgical Treatment of Tremor: Presentation of Case, with Motion Pictures. DR. PAUL C. BUCY.

About two years ago I demonstrated before this society a patient with left hemiballismus in whom the involuntary movements were completely relieved by extirpation of the contralateral precentral cortex (Surgical Treatment of Unilateral Choreoathetosis, ARCH. NEUROL. & PSYCHIAT. **43**:1274 [June] 1940). At that time there was in the hospital a young man who had suffered from left unilateral parkinsonism for many years and in whom I had also extirpated the right precentral cortex. This evening I present the latter patient to you. The case is of particular interest from two points of view, the effect of the extirpation on the tremor and its effect on voluntary movement and spasticity in the extremities.

This man was operated on in December 1939. The representation of both the left upper and the left lower extremity in areas 4 and 6 of the right precentral cortex was removed. The tremor was immediately abolished and has remained so. This leaves little doubt that the involuntary movements of parkinsonism are mediated by efferent fibers descending from the precentral region, just as are the involuntary movements of athetosis and intention tremor.

Prior to the operation there was good voluntary power in the left arm and leg, although this was rendered practically useless in the arm by the continuous violent tremor. He walked with a definite, though slight, limp. There was mild rigidity of the extremities. The tendon reflexes were slightly hyperactive, and Babinski's sign was present on the left side.

At present the patient walks well but with a more marked limp than before the operation. The leg is spastic, and he circumducts it in walking. The foot is not dragged. He is able to, and frequently does, walk without undue fatigue. The arm is much more severely involved. Movement at the shoulder is fairly good, and he is able to lift the hand well above his head. However, at the end of this movement, when the muscles are placed under pronounced stretch, clonus develops. Movement at the elbow is possible but is slower and less extensive. There is almost no voluntary movement at the wrist or of the fingers, although when the elbow is flexed the wrist and fingers also flex and in this manner he is able to hold objects, such as a package of cigarets. There is marked clasp knife spasticity in the left upper extremity, especially in the flexor muscles. However, as he walks the arm hangs extended at his side and flops. Clonus in the flexors of the wrist and fingers is readily elicited by passive stretching. All tendon reflexes are greatly exaggerated on the left. The Babinski and Oppenheim signs are present on the left, but there is no disturbance of the abdominal reflexes.

It is thus clear that destruction of the precentral cortex is capable of producing spastic hemiparesis. This and other evidence lead one to conclude that there is considerable bilateral cortical innervation of the lower extremities, whereas the amount of innervation from the ipsilateral cerebral cortex to the upper extremity is less than that to the lower extremity. In some measure this is more apparent than real. In both extremities the greatest deficiencies are at the distal joints. In the upper extremities, in which the principal function is prehension, this deficiency is obvious. In the lower extremities, which are used principally for support and walking, a rigid extremity which can be moved from the hip is very useful indeed.

This case and others like it leave no doubt that the precentral cortex controls the postural reflexes and that the destruction of this region alone, quite apart from any associated damage to the basal ganglia, is capable of producing spasticity.

Pathologic Changes in the Central Nervous System in Experimental Electric Shock. Dr. Gert Heilbrunn (by invitation) and Dr. Arthur Weil.

This paper will be published in a later issue of the Archives.

Autonomic Indications of Excitatory and Homeostatic Effects on the Electroencephalogram. Dr. Chester W. Darrow, Dr. Hudson Jost, Dr. Alfred P. Solomon and Dr. John Charles Mergener.

By simultaneously recorded electroencephalographic, palmar galvanic (sweating) and systolic blood pressure reactions of selected subjects with high "per cent time alpha" to a variety of stimuli, it is confirmed that beta potentials tend to increase and alpha potentials tend to decrease after stimulation. Correlation, r, of the galvanic response with increase of beta potential is + 0.509, with decrease of alpha potential is + 0.500 and with decrease of delta potential is + 0.238. In contrast to these results, the correlation of rise in blood pressure with increase of beta potential is — 0.238, with decrease of alpha potential is — 0.376 and with decrease of delta potential is + 0.445.

It is inferred from these relations that a stimulus must have two effects: (1) excitation and (2) a homeostatic action of the concomitant change in blood pressure. If this is the case, it should be possible by subtracting an index of homeostatic influence from an index of concomitant excitation to obtain improved correspondence between autonomic and electroencephalographic changes. Assuming an index of 1 for both measures, the change in blood pressure is subtracted from the percentage of galvanic change and correlations, r, are obtained, with increase of beta potential of + 0.575, with decrease of alpha potential of + 0.605 and with decrease of delta potential of + 0.439. By combining beta with alpha and delta frequencies a total correlation with galvanic minus blood pressure change of + 0.752 is obtained.

These results suggest the operation of two possible neurophysiologic mechanisms: (1) the intrinsic vasomotor mechanism regulating cerebral circulation, in the case of the alpha frequencies, and (2) the local cerebral activity, particularly that relating to muscular tension, in the case of the beta frequencies. These mechanisms are, furthermore, affected in corresponding fashion by numerous other physiologic conditions. Not only local cerebral excitation and fall in blood pressure but carbon dioxide tension, anoxia, trauma, lowered p_H, convulsions and sleep are shown by extensive reference to the literature to be associated with both cerebral vasodilatation and decreased alpha potentials. Conversely, cerebral vasoconstriction and increase of alpha potential tend to occur concomitantly under the opposite physiologic conditions. The possible basis of this relation is considered. The view that beta activity is related to sensory motor function is also supported.

The results of the experiment are thus neurophysiologically accounted for.

DISCUSSION

Dr. W. S. McCulloch: I am particularly impressed with the extreme difficulty one encounters in presenting anything in the way of mathematical treatment of neurologic or medical problems. The correlation Dr. Darrow and his associates

have established could doubtless be bettered by more elaborate formulas. The correlation is unquestionably significant. I heartily agree with them in ruling out the slower, chemical changes in the brain. The slow potentials which inhibit the cortex have been considered by some as axonal, spikelike potentials and by others as peculiar properties of the cell body. Neither explanation has been satisfactory. The possibility of vascular potentials does not seem a probable answer to the problem. In general, if one has a small electrode and comes down on a blood vessel by mistake, one does encounter slow frequencies—sometimes only deviation in pulse pressure, due to the movement of the electrode; it is incumbent on one, however, to rule out the possibility of contributions from the blood vessels.

DR. DAVID SLIGHT: I should like to ask about two matters that are not clear to me. The galvanic cutaneous change occurs in a clearcut fashion after a measurable latent period, whereas the point of change in the electroencephalogram following stimulation is often difficult to determine, except in relation to opening and closing the eyes. How, then, does Dr. Darrow determine the point in the electroencephalogram for correlation with the galvanic cutaneous change? Also, I should like to ask whether the electroencephalographic changes are noted only for the same period as the galvanic cutaneous change, or, if not, for what length of time?

DR. CHESTER W. DARROW: With regard to the vasomotor effect of hypothalamic excitation, I hope I did not give the impression that we assumed we were recording only effects of vasomotor activity in the brain. There is no question that in addition there are potentials generated by activity of the brain itself which are picked up and recorded in the electroencephalogram. The relation of autonomic changes to the delta waves, which so often have been identified with emotion, is not so clear, although it is apparent that there is some relation.

In answer to Dr. Slight, I may say that the latent period of two to three seconds in the case of the galvanic response has to be taken into consideration in relating the autonomic and the electrocortical records. In plotting the curves of simultaneous activity we have to move the autonomic record forward two or three seconds to make the curves correspond. There is a similar instrumental delay in the case of blood pressure. However, in the calculation of reaction to stimulation we have simply used the three seconds before as compared with the three seconds after the point of excitation, as determined by inspection of the autonomic and electroencephalographic records. One can readily observe and allow for the latent time prevailing in a given section of the galvanic record.

I am pleased with Dr. McCulloch's remarks, particularly in view of the fact that he and his collaborators have done some of the most significant work on hydrogen ion concentration and corticothalamic relations.

Untoward Effects of Dilantin on Patients with Epilepsy. DR. ISADORE FINKELMAN and DR. ALEX J. ARIEFF.

Forty-one patients with epilepsy were treated with dilantin sodium (sodium diphenylhydantionate) according to the method of Merritt and Putnam.

All the patients showed some side effects of the drug, chiefly on the nervous system. Mild symptoms of apprehension and irritability were present in 21 patients. More severe symptoms appeared in others, consisting of a paranoid confusional state in 6 patients, encephalopathy in 4, status epilepticus in 2 and peripheral neuritis in 1. Other side effects on the nervous system were ataxia of all degrees, vertigo, blurring of vision, nystagmus and tremors, insomnia and somnolence. (One patient was thought to have a cerebellar tumor until the history of dilantin medication was considered.) Of particular interest in relation to the cardiovascular system was electrocardiographic evidence of involvement of the heart in 32 patients, with subjective complaint of precordial pain in 5 of them. One patient had edema of the legs. Toxic effects were also noted in the gastrointestinal system, and in a few patients the symptoms simulated an acute abdominal condition. Loss in weight occurred in 11 patients. Six patients had a cutaneous rash, and in 1 the rash and fever simulated scarlet fever. Albuminuria occurred in 6 patients. Toxic effects on the blood consisted of eosinophilia in 9 patients,

secondary anemia in 3 patients and basophilia in 4 patients. Increase in the blood phosphatase was present in 10 patients.

Of the 41 patients, only 7 remain under active therapy with dilantin at the time of this report. Six have had remission from seizures of from ten to seventeen months, and 1 has been free from seizures for about two months. With the remainder, 34 patients, the therapy was discontinued because of severe toxic effects or ineffectiveness of treatment.

DISCUSSION

DR. MILTON ROSENBAUM, Cincinnati: Most physicians who have had experience with dilantin are well aware of its toxic properties, but it would seem, to me at least, that the toxic symptoms which may result from dilantin are not as frequent or as severe as the authors have indicated. I have had the pleasure and opportunity of having seen many of Merritt's patients who were treated with dilantin, and I believe that the toxic symptoms encountered in his large group were much milder than those in the authors' group. Merritt, I believe, described mild toxic symptoms as having occurred in about 15 per cent of his patients and more severe toxic symptoms in 5 per cent. The usual toxic signs and symptoms encountered are ataxia, dizziness, staggering, diplopia, nystagmus, nausea and vomiting, and at times a slight fever. These symptoms usually occur about the tenth day of treatment, and in the majority of cases will disappear on decreasing the dose of the drug. After the disappearance of these symptoms, the drug may then be resumed either in a reduced dose or, in many cases, in the original dose without the recurrence of toxic symptoms. Some patients are not able to tolerate the drug even in very small doses, but such cases are rare.

The authors stated that "status epilepticus" was a toxic symptom of dilantin in some of their cases. After all, "status epilepticus" is a well known manifestation or symptom of epilepsy itself, and I do not see how the occurrence of such an outbreak can be attributed to dilantin just because the patient happens to be using the drug at the time. Certainly, this condition occurs in patients who are being treated with other anticonvulsant drugs, and such drugs have not been accused of the responsibility. All know, furthermore, that "status epilepticus" may occur if dilantin is either suddenly withdrawn or substituted for another anticonvulsant drug which is suddenly withdrawn before the dilantin can be accumulated in the body. I should also question the statement that dilantin itself produced the peripheral neuritis which the authors listed as a toxic manifestation of the drug.

The authors referred to a case reported by Dr. Charles Aring and myself as also illustrating the toxic effects of the drug (Ingestion of Large Doses of Dilantin Sodium, ARCH. NEUROL. & PSYCHIAT. **45**:265-270 [Feb.] 1941). The case was that of a boy who took large doses of dilantin sodium (60 and 70 capsules, or 6 and 7 Gm.) over a short period (ten hours) as a suicidal attempt. True, rather severe toxic symptoms developed, but he recovered; the case thus illustrates the high safety factor of the drug.

The mild toxic symptoms encountered are well compensated for by the striking and gratifying anticonvulsant action of the drug in many cases.

PHILADELPHIA NEUROLOGICAL SOCIETY

BERNARD J. ALPERS, M.D., *Presiding*

Regular Meeting, Oct. 24, 1941

Certain Epidemiologic Aspects of Poliomyelitis. DR. JOSEPH STOKES JR.

Character of the Poliomyelitis of 1940-1941. DR. PASCAL LUCCHESI.

There has been no epidemic of poliomyelitis in Philadelphia this year, for 78 cases, to date, can hardly be called an epidemic. The state, however, has had an outbreak of epidemic proportions. The fact that Philadelphia escaped an

epidemic this year can be attributed to the increased incidence of poliomyelitis in this city since 1932, with the consequent greater immunization of susceptible persons. A slide is shown to demonstrate the more than usual number of cases in 1935, 1937 and 1939. In 1939, 178 patients were treated at the Philadelphia Hospital for Contagious Diseases, but there was not the usual confusion and excitement in the city, for there was little newspaper publicity. In succeeding slides are compared the number of cases at the Philadelphia Hospital for Contagious Diseases in 1932, 1939 and 1941, respectively.

A definite tendency to shift from the 1 to 5 year group to the 5 to 10 and the 10 to 15 year groups was evident, and the death rate was higher among persons under 1 year and over 20 years of age. The death rate was 7.89 per cent in 1932, 3.37 per cent in 1939 and 1.11 per cent in 1941, indicating a tendency toward greater mildness of the disease. Paralysis occurred in 192 of 304 cases in 1932, in 160 of 178 cases in 1939 and in 60 of 78 cases in 1941. However, the paralysis in 1941 was not as extensive or severe as in previous years. The percentage of cases in which respirator treatment was required was 5.59 in 1932, 6.18 in 1939 and 7.69 in 1941. However, the death rate of respirator patients was 58.82, 54.54 and 1.28 per cent, respectively.

There is no evidence to show that Negroes are less susceptible, for in Philadelphia for 1932, 1939 and 1941 the average Negro population was 12.8 per cent, whereas the percentage of cases of poliomyelitis among them was 14.4.

Cases of the spinal types predominated, the percentages being 90.1, 83.75 and 93.67 in 1932, 1939 and 1941, respectively.

The peaks of the outbreaks were reached in September, dropping about the third week.

The tonsils were absent in 23.2, 33.3 and 36.4 per cent, respectively, of patients without paralysis. But the absence of tonsils seems to favor the development of the bulbar or the bulbospinal type.

DISCUSSION ON PAPERS BY DR. STOKES AND DR. LUCCHESI

DR. F. H. LEAVITT: Can Dr. Lucchesi say anything about the cell count of the spinal fluid in the 1941 group?

DR. PASCAL LUCCHESI: The cell counts were not as high in the 1941 group as they were in the 1932-1939 groups. The highest cell count which my associates and I saw this year, if I remember correctly, was about 700 per cubic millimeter; that is a count characteristic of the meningitic type. We had 3 or 4 cases in which this high count was present; the count was usually lower. The predominant cell was the lymphocyte.

DR. F. H. LEAVITT: Were there any cases of total poliomyelitis?

DR. PASCAL LUCCHESI: We had 2 cases of the meningitic type in which the cell count was chiefly on the polymorphonuclear side for about a week, but usually it shifted to the lymphocytic side.

DR. J. W. MCCONNELL: Of interest to me was the number of cases that occurred in one dwelling.

I was a member of the committee which investigated the epidemic in Pennsylvania in 1916. My territory was Clarion and Elk Counties, where there were isolated villages, made up of the most miserable shacks, and many cases were found in those houses. I remember one house that held a family of 7, all of whom were stricken with the disease. There were numerous instances in which 2 in a family were ill. Later on, in going over to Du Bois, Pa., we found a great number of instances in which there was more than 1 case in a family.

Among my personal experiences, I recall a man who had poliomyelitis as a boy of 14 and recovered fairly well. He was left with paralysis of two muscles: one in the upper portion of the left arm and the other in the lower part of the right leg. He married later, and his son, at almost the same age as the father, contracted poliomyelitis and recovered with the exception of two muscles, which were not, however, distributed as were the father's.

DR. PASCAL LUCCHESI: In 1939 we had 3 patients at the hospital who were pregnant and had poliomyelitis. These patients were delivered, 2 of them, I think, at the Pennsylvania Hospital and 1 at another hospital. As far as I know, the mothers and newborn infants were perfectly normal.

With reference to the multiple cases of poliomyelitis that Dr. McConnell mentioned: In 1916 there were 14 families and in 1932 25 families with multiple cases in Philadelphia. This year we have had 2 families. In one of the families the paralysis was in the left leg in 1 of a set of identical twins and in the right leg in the other.

DR. M. K. MYERS: Concerning the epidemic of 1916, I think that 14 families in which there were multiple cases is a rather low figure. I investigated several cases in Philadelphia in 1916; I was, however, struck by what seemed to be the low incidence of multiple cases in the families of Philadelphia.

I believe that during the epidemic of 1916 many cases of the so-called abortive form were probably not recognized and therefore were not counted. I was associated with the department of health as medical inspector at that time, and I remember the epidemic well. It was very severe, and by the time the inspectors reached the homes most of the children had already shown the paralysis. Of course, it is probable that many cases of the mild and of the abortive form were overlooked. Dr. Lucchesi made the statement that poliomyelitis this year was much milder and the effects of treatment seemed much better than in former years. This does not imply that future epidemics may not be severe.

May I ask Dr. Lucchesi whether there was any change in the method of treatment—whether the sulfanilamide products were used in these cases?

DR. PASCAL LUCCHESI: I do not believe because the disease this year was mild that poliomyelitis is really becoming a mild disease. One does not know just how severe it may be in succeeding years.

Specific therapy with sulfanilamide or its derivatives was not employed. Usually the spinal tap was made for diagnostic purposes. Concerning the multiple cases, Dr. Myers, in 1916, as you know, the disease was usually diagnosed "poliomyelitis with paralysis," and there were very few cases of the abortive form. The same thing happens even now. Of course, the incidence in families may be low. Some authorities claim that there are five times as many cases of the nonparalytic or abortive type during periods of increased incidence as there are of the paralytic form, and it can readily be seen that there would probably be many more than is indicated by the incidence here.

DR. S. B. HADDEN: The presentation of Dr. Stokes is valuable in that he presents his observations and interpretations to assist in crystallizing opinion relative to the epidemiology of infantile paralysis. For far too long infantile paralysis has been regarded as an air-borne disease, despite the fact that it is most unusual to see 2 cases occurring simultaneously in a family. Only recently I heard Dr. W. S. Cornell, the school physician of Philadelphia, report to the Committee on Poliomyelitis that in his thirty some years as a school physician he had seen 2 cases occur in a schoolroom on only one occasion, and that was during the recent period of increased incidence in Philadelphia.

Dr. Stokes's unusual observation is a most important one and adds its weight to the evidence already piling up that there is in all probability an insect or other vector concerned in the spread of poliomyelitis and that precautions such as those advised for typhoid or enteric infections might be far more productive of beneficial effects than the present attitude toward the disease.

DR. F. H. LEWEY: One difficulty in poliomyelitis research is that no animal seems to contract poliomyelitis spontaneously. Animals are inoculated with doses far beyond the amount that can possibly be ingested or inhaled under natural conditions.

Does Dr. Stokes know of instances in which poliomyelitis has spread directly from monkey to monkey? The possibility of transmitting poliomyelitis through flies from the feces of infected animals to healthy monkeys was reported by Dr.

Simon Flexner more than thirty years ago. However, sufficient proof has not been collected to show that this is the common way of transmitting poliomyelitis in human beings.

DR. I. J. WOLMAN: It has been found impossible to transmit experimental poliomyelitis from monkey to monkey by transfusions of blood. All the experimental work furnishes evidence that in these animals the virus spreads through the nervous system.

For example, Howe and Bodian recently demonstrated that when the proximal end of a cut sciatic nerve is moistened with virus for a moment or two the animal becomes ill with poliomyelitis several days later.

The virus of poliomyelitis is a stable one. It can be subjected to chemical manipulation in the laboratory for two or four days without appreciably losing its virulence. It can resist ether, phenol and toluene. It resists the concentration of chlorine that is ordinarily used in purifying drinking water. It is susceptible to ultraviolet light and the oxidizing agents, such as potassium permanganate and hydrogen peroxide. It is destroyed by pasteurizing temperatures and circumstances.

Sabin and Ward have reported that the virus is always present in the contents of the colon of the patients, though not in the contents of the ileum. They failed to find it in the wall of the colon but did find it regularly in the wall of the ileum. They suggest that the virus multiplies in the wall of the ileum and is excreted from the ileum into the stool.

Kramer reported that virus was found in the stool of a healthy person six months after contact with an infected patient. Whether the virus multiplies in the tissue proper of the wall of the ileum or in the sympathetic nerve portion is not known.

It is known that in human poliomyelitis the spleen is enlarged and the lymph nodes are swollen. In the patients this may be a manifestation of early antibody response.

BERNARD J. ALPERS, M.D., *Presiding*

Regular Meeting, Nov. 28, 1941

Compression of the Spinal Cord by Sarcomatous Degeneration in the Course of Osteitis Deformans (Paget's Disease) of the Vertebrae: Report of a Case. DR. GABRIEL A. SCHWARZ and DR. PHILIP J. HODES.

Compression of the spinal cord in osteitis deformans of the vertebrae has been reported to occur by compression, collapse, fracture or dislocation of the diseased vertebrae, by overgrowth of the pathologic bone into the vertebral canal or by any combination of these abnormal conditions (Schwarz, G. A., and Reback, S.: *Am. J. Roentgenol.* **42**:345 [Sept.] 1939).

We had the opportunity to observe a case in which compression of the spinal cord resulted from an osteogenic sarcoma developing in vertebrae affected by osteitis deformans. We further witnessed the eradication of the compressive effect by roentgen irradiation.

REPORT OF CASE

A white man aged 70 was admitted to the neurologic service of Dr. W. B. Cadwalader in the Hospital of the University of Pennsylvania on March 19, 1940, having been referred by Dr. Adolf Creskoff. He began to have intermittent pain in the lower part of the back in 1936. In January 1940 he noted some weakness in his lower extremities. This progressed rapidly, so that by the time he was admitted both lower extremities were completely paralyzed. For a few weeks preceding his admission he suffered from urinary retention and obstipation.

Examination revealed depressed areas in the frontoparietal regions of the skull, notable thickening and bowing of the left tibia, an emphysematoid deformity of the chest, vascular hypertension, marked peripheral arteriosclerosis and bilateral

inguinal hernia. There were spastic paraplegia and a sensory level at the eleventh or twelfth thoracic dermatome.

There was complete block of the spinal subarachnoid pathways. The cerebrospinal fluid contained 140 mg. of protein per hundred cubic centimeters.

Roentgenograms of the skull, left tibia, vertebrae and sacrum showed changes typical of Paget's disease. Dr. Eugene Pendergrass expressed the belief that the bony changes in the region of the lower thoracic vertebrae were due to malignant degeneration occurring in the course of osteitis deformans.

Treatment was started with roentgen irradiation through various portals over the lower thoracic portion of the spine. Clinical improvement began soon thereafter.

A second lumbar puncture, performed on Feb. 18, 1941, showed no spinal subarachnoid block. The protein content of the spinal fluid was now only 45 mg. per hundred cubic centimeters.

When last examined, on Sept. 19, 1941, the patient was able to walk alone without support. The results of all sensory tests were normal except for slight impairment of vibration sense in the right lower extremity. The patient had no other complaint except a slight pain across the lumbar region.

Comment.—The various factors associated with the development of sarcomatous degeneration in osteitis deformans are reviewed. The diagnosis of malignant degeneration in this case rested entirely on roentgenographic findings. The decision not to perform a laminectomy was based on the poor physical condition of the patient. It is felt that this consideration should determine the use of laminectomy in any case of osteitis deformans with compression of the spinal cord, rather than the uncertainty as to whether or not the surgical trauma would bring about or exaggerate the growth of a sarcoma.

Diabetes Insipidus and Other Unusual Complications of Acute Purulent Sinusitis: Clinicopathologic Study of a Case. Dr. J. C. Yaskin, Dr. F. H. Lewey and Dr. G. Schwarz.

This article will appear in a later issue of the Archives.

Pathologic Changes Revealed by Exploratory Laminectomy in Two Cases of Amyotrophic Lateral Sclerosis. Dr. Temple Fay.

In 2 cases of typical amyotrophic lateral sclerosis exploration of the high cervical region was carried out. In the first case, that of Y. D., laminectomy on Sept. 14, 1938, revealed large, bulging epidural veins constricting the canal and compressing the cord posteriorly. Biopsy showed inflammatory tissue, polymorphonuclear infiltration and thrombophlebitis. In the second case, that of F. D., exploration, on July 16, 1941, revealed an anomalous vein compressing the upper cervical portion of the cord, with arachnoid adhesions and compression of the cord posteriorly against the atlas. Biopsy showed "thrombophlebitis." There was a small area of circumscribed epidural inflammation beneath the fifth, sixth and seventh cervical laminas. In the second case relief of pressure from the varicose veins was afforded, and the patient has made a steady recovery, with return of power, particularly in the upper extremities. He was presented four and one-half months after operation.

DISCUSSION

Dr. R. L. Masland: I should like to ask Dr. Fay whether any disturbances of sensation were observed in either of these cases. Ordinarily with compressive lesions of the cord there are associated disturbances of the tract or of the roots. If there was none how is that explained?

Dr. A. M. Ornsteen: Amyotrophic lateral sclerosis is at best an unsatisfactory diagnosis, so that any effort to weed out atypical cases for study is welcome, especially if the approach is at the same time a therapeutic one, with occasional benefit to the patient. For this effort Dr. Fay should be given credit, particularly

for his attempt to identify a clinical entity, which he calls meningorachidian thrombophlebitis, or the Spiller syndrome. Because he has satisfied himself that such a pathologic condition exists in atypical cases of amyotrophic lateral sclerosis, and because the patients he presents have shown improvement, the entity may have to be accepted. In addition, we, the members of this society, appreciate his honoring the name of our revered friend, Dr. William G. Spiller.

The syndrome of amyotrophic lateral sclerosis is looked on as a distinct entity, with characteristic features and clinical course, but heretofore meningorachidian thrombophlebitis has not been part of the pathologic changes reported. Since Dr. Fay believes that such a condition explains the syndrome in the cases in which he operated, I should like to know what the difference, if any, in the clinical picture of the two types of the disease may be.

DR. J. C. YASKIN: I think it was Dr. Wechsler who, in formulating last year the thesis of treatment of amyotrophic lateral sclerosis, stated that the condition is probably not a distinct disease entity but represents a variety of disorders and that some of these conditions are amenable to his treatment. Dr. Fay now calls attention to another subgroup of cases in which the disturbance may be due to a compressive lesion. I am in agreement with Dr. Ornsteen that any effort which brings one a little closer to understanding of these diseases, and which may be helpful in a few cases, is worth while.

The concept of amyotrophic lateral sclerosis is somehow difficult to reconcile with that of a compressive lesion. Dr. Masland has already pointed out the conspicuous absence of both pain and anesthesia in the usual cases. Also, in many cases the disorder begins not with involvement of the spinal cord but with lesions in the medullary nuclei and higher in the brain stem. For instance, not a few have seen the lesions begin in the peroral region and the tongue. It is difficult, therefore, to correlate the picture in these cases with that of amyotrophic lateral sclerosis due to a compressive lesion at the spinal level.

Even if one takes the more typical compressive conditions of the higher regions of the spinal cord, for instance, the relatively rare hypertrophic cervical pachymeningitis, one gets a vastly different picture from that in the great majority of cases of amyotrophic lateral sclerosis. In fact, the sensory picture predominates in those cases. It is pain first and foremost, and later involvement of the upper and lower motor neurons.

DR. TEMPLE FAY: I think Dr. Yaskin's discussion overemphasized compression and thus distorted the issue. I stated that perhaps the underlying degeneration in the cord might somehow be explained on a mild compression basis, but not, certainly, the whole picture. I have a strong feeling that this entire syndrome is due to an infectious agent, the venous stasis playing an important secondary part in the disturbance of the cord and its function.

I want first to answer the question about the sensory changes. I chose only 2 cases because both of them fulfilled the criteria for the purely motor, or Charcot, type of amyotrophic lateral sclerosis and there were no sensory changes and no history of sensory involvement at any time. Furthermore, the weakness and the progression of symptoms were classic, and the fibrillary tremors, I believe, added to the diagnostic phase.

I believe that Charcot picked a classic syndrome out of a huge group of demyelinating types of progressive spastic paraplegia and called one of them amyotrophic lateral sclerosis. Jelliffe has pointed out a remarkable group of 90 cases of amyotrophic lateral sclerosis, supposedly true in their type, which were precipitated or caused by trauma.

DR. J. C. YASKIN: Are inflammatory lesions conspicuous by their absence within the cord?

DR. TEMPLE FAY: Again, I think I pointed out that the inflammation resided in the epidural veins and that the venous stasis was, in my opinion, the factor responsible for the involvement of the cord. Certainly, the pathologic picture of the living tissue is far different than that of dead tissue, and the neuropathologist

will never realize from the study of shrunken, formaldehydized tissue how large the epidural veins may become when engorged with blood or how much compression is possible until he sees these veins at work on the tissues themselves, as the neurosurgeon sees them during life. The pressures of coughing and straining modified by posture, combine to establish a mild, constant compression, which, in my opinion, can produce chronic progressive symptoms. I am going to make a plea that the case of amyotrophic lateral sclerosis be considered from a neurosurgical standpoint, when and if the neurologist can offer no better solution, because of the otherwise certain fatal outcome. If my experience holds true for other ascending bulbar types, there is, at least, a chance to stop the process by decompression of the foraminal area and by attention to the infection.

DR. F. C. GRANT: Was the thrombosis confined to the first of the six cervical segments?

DR. TEMPLE FAY: In my second case there were at least three segments in which there was no involvement, and then there was a patch as big as a dollar, which quite circumscribed the fifth, sixth and seventh segments; the other lesion was just in the foraminal region. I don't believe that there is anything characteristic about the location of the lesions.

Clinicopathologic Study of Alzheimer's Disease: Report of a Case. DR. F. H. LEAVITT and DR. F. H. LEWEY.

A case of Alzheimer's disease is described, the course of which differed from the usual one in its long duration—forty-three years if two periods of depression with severe headaches are considered part of the final disease, otherwise thirteen years. A pronounced parkinsonian syndrome, with contractures of the arms and legs developed. During the last three years of her life the patient was in a state of decerebrate rigidity and gave no evidence of being a human being. Necropsy revealed severe atrophy of the brain, with enormous hydrocephalus and lobar atrophy. Senile plaques were abundant over all the cortex. The majority of nerve cells had disappeared, and those preserved showed senile fibrillary changes. The basal ganglia were in the same state of atrophy. Senile plaques and fibrillary changes were present in the corpus striatum and the basal nuclei, while the cells of the globus pallidus exhibited fatty degeneration.

Paralysis agitans, the subcortical variant of Alzheimer's disease, is frequently followed by the cortical form. The reverse sequence, as evidenced by our patient, is rare; in fact, only 1 case seems to be on record, and that of a mild form. The same is true as to the severe senile atrophy of the basal ganglia in Alzheimer's disease.

DISCUSSION

DR. M. T. MOORE: Were there choreoathetoid movements at any time? It is evident from the excellent sections which have been shown that the putamen and the caudate nucleus have undergone severe atrophy, associated with internal hydrocephalus, a state of affairs which resembles in part the changes in Huntington's chorea.

DR. B. J. ALPERS: Is it inferred that this woman had Alzheimer's disease from the time of the first mental disturbance?

DR. F. H. LEAVITT: I can state that at no time did the patient exhibit any choreoathetoid movements. As to Dr. Alpers' question whether this patient was suffering with Alzheimer's disease from the time of the first mental disturbance, in 1887, my answer would be "conjectural." In that year she had what was described as a manic attack, but it was the only one of which there was any record. The recurrent and increasing psychotic episodes were all of a depressive type. It is known that Alzheimer's syndrome is frequently initiated by episodes of depression.

DR. F. H. LEWEY: The patient had a manic phase. I did not know that previously; I knew only of the depressive phases, and I went quite out of my way to

find whether nonfamilial depressions are known in Alzheimer's disease; I was amazed to find that a number of cases are on record. An emotional phase of depressive nature has been repeatedly described as the initial phase of Alzheimer's disease.

Foster Kennedy Syndrome Associated with Non-Neoplastic Intracranial Conditions: Report of a Case. Dr. H. Edward Yasskin, Camden, N. J., and Dr. N. S. Schlezinger.

Two cases were presented in which the neuro-ophthalmologic observations conformed with the syndrome described by Foster Kennedy. This syndrome has generally been considered as diagnostic of basotrontal expanding lesions. The cause of the symptom complex in both cases was non-neoplastic. The neuroretinal disturbances were a result of compression of the optic nerves by sclerotic vessels, a condition proved in the first case and probable in the second. The presence of a binasal field defect associated with the Foster Kennedy syndrome necessitates consideration of the presence of sclerotic internal carotid or anterior cerebral arteries. Some cases reported in the literature also indicate that the syndrome may be caused by intracranial neoplasms which are not situated in the anterior fossa. In all doubtful cases of neoplasm of the anterior fossa in which a Foster Kennedy syndrome exists, one should resort to arteriographic or cerebral air studies before recommending craniotomy.

DISCUSSION

Dr. J. C. Yaskin: The interpretation of slight degrees of papilledema should be taken with considerable caution by the neurologist and the neurosurgeon. I should like to mention in this connection a recent case of binasal hemianopia with so-called papilledema and some atrophy. The patient had a moderate degree of hypertension and extremely calcified carotid arteries, and air studies revealed nothing significant. Both papilledema and optic nerve atrophy occur in the course of arachnoiditis. Patients with this condition occasionally require surgical intervention, even if the cause is syphilis, when they fail to respond to antisyphilitic treatment.

Dr. Temple Fay: Would Dr. Yasskin restate what part the anterior cerebral arteries played in the defect in the first case?

Dr. H. E. Yasskin, Camden, N. J.: In answer to Dr. Fay, I can only repeat the surgeon's report after operation. Both he and his assistant observed as they elevated the right frontal lobe that the right optic nerve was atrophic and tightly stretched over a large vessel approximately one-half the diameter of the little finger of an adult. It was their impression that the vessel was the anterior cerebral artery. A similar situation was discovered on the opposite side.

Dr. Temple Fay: I bring the point up because I do not know of any instance in which I have seen an anterior cerebral artery which could encroach on the optic nerve. I have seen an anterior communicating artery which could and did overlie the chiasm, but as for the two anterior cerebral arteries involving the nerve itself, I confess that has not come under my observation as yet, either in the dissecting room or on the operating table.

I should raise the question whether either of these patients had the Foster Kennedy syndrome. I do not believe that papilledema of 2 D. is up to the level of unquestioned choking. I have heard Dr. de Schweinitz argue that neuroretinitis and papilledema cannot be clearly differentiated up to 2 D.

Dr. John C. McNerney: I remember the first case from writing it up and drawing a diagram immediately after the operation. I do not recall the detailed anatomic relations now, but I distinctly remember the vessel. I should say it was one-quarter the size of my little finger, and it was thick and firm. I am sure it was the anterior cerebral artery, because vizualization was excellent and the

anterior communicating and the internal cerebral artery were identified. Dr. Yaskin will find the diagram on the operative note for verification.

DR. H. E. YASSKIN, Camden, N. J.: As to Dr. Fay's point as to whether or not we were dealing with optic neuritis or papilledema, most of the men on the staff were convinced we were dealing with choked disk, but I must say this: These 2 patients were observed by competent neurologists and ophthalmologists in two different institutions, all of whom were convinced that the condition was papilledema in the eye in question. I cannot see that any exception should be taken to our diagnosis of Foster Kennedy syndrome, when it was the consensus of all these examiners that this syndrome was present in each case.

Cephalogyric Reactions. DR. E. SPIEGEL.

Bilateral section of the eighth nerve in decerebrate cats reverses the direction of the rotation of the head produced by a direct current stimulus that flows transversely through the skull, the rotation being directed toward the anode before and toward the cathode after section of the eighth nerves. After unilateral section of the eighth nerve in decerebrate cats, the rotation toward the anode is usually preserved when the cathode lies on the normal side, while the rotation toward the cathode may appear if the cathode lies on the side of operation. On bipolar monaural stimulation one observes rotation to the opposite side as long as the eighth nerves are intact and, after the corresponding nerve has been cut, to the side of operation. The rotation to the anode on transverse binaural stimulation with direct current stimulus or to the opposite side on bipolar monaural stimulation with direct current, rectangular alternating current or faradic current (contralateral cephalogyric reaction) is a vestibular reaction. The rotation toward the cathode and to the same side (ipsilateral cephalogyric reaction) is due to stimulation of afferent fibers in the roots of the fifth, and of the ninth and tenth nerves, respectively; it may appear not only when the vestibular nerves are cut but when their excitability is depressed. The centers of the ipsilateral cephalogyric reaction lie in the medulla oblongata and the pons. The reaction elicited by stimulation of afferent trigeminal fibers uses efferent fibers descending into the spinal cord; an efferent pathway along the accessory nerve could not be established with certainty for this part of the reaction. For the ipsilateral rotation elicited by stimulation of the afferent fibers of the ninth and tenth nerves efferent pathways could be demonstrated using the accessory nerve, as well as fibers descending into the spinal cord.

Book Reviews

Epilepsy and Cerebral Localization. A Study of the Mechanism, Treatment and Prevention of Epilepoic Seizures. By Wilder Penfield, M.D., and Theodore C. Erickson, M.D. Chapter XIV by Herbert H. Jasper, M.D. Chapter XX by M. R. Harrower-Erickson. Price $8. Pp. 623, with 163 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This book has its roots in an observation of Hippocrates on crossed convulsive movements, in the studies on stimulative epilepsy of Fritsch and Hitzig and in the keen clinical studies of Hughlings Jackson and Charles Sherrington. It is dedicated to the last two investigators.

By studying the physiologic reactions of the brains of conscious patients exposed at operation, Penfield and his associates have answered questions which for centuries have been asked in vain. They have observed the appearance and the circulation of the brains of patients before and during convulsions; they have stimulated various areas of the cortex, recorded the responses and correlated these with the patient's spontaneous seizures. The reports teach a great deal about the anatomic significance of the constituent manifestations of seizures and about the physiology of the brain of epileptic, and perhaps of normal, persons. Equally valuable are the authors' painstaking histologic studies on brain injuries, the epileptogenic lesions whose slowly enlarging border of cell injury and destruction leads finally to seizures. The authors make a good case for excision of any epileptogenic cicatrix which involves the brain, though other neurologists might not agree that surgery offers the sole hope of permanent relief. In addition to an unstated number of cases which were excluded because the patients were taking dilantin sodium, cicatrices were excised from the brains in 165 cases. Of these, freedom from attacks was observed in 21 per cent and at least 50 per cent improvement in 68 per cent. In comparison, the report on cases of expanding lesions is inadequate. Of 703 cases of verified tumors, a follow-up report is given for only 83. Of the 56 cases in which seizures occurred before operation, there was freedom from attacks afterward in 25 per cent, but of 27 in which previous seizures did not occur, attacks began after the operation in 44 per cent. Readers of the ARCHIVES are familiar with the trend of these various studies, reports on which have appeared in this and in other neurologic journals during the past dozen years. All this original work is beautifully illustrated with scores of photographs and drawings.

Penfield's long-standing interest in the cerebral circulation in cases of epilepsy makes his opinion peculiarly important. As early as 1930 the hypothesis had been advanced ". . . that a vasomotor reflex secondary to this traction [on blood vessels in a scar] is responsible for the initiation of the convulsive seizures." Again, "The epileptic brain is subject to local vasomotor reflexes such as have never been described in the normal human brain." In the present volume is the flat statement (page 173): "There is no evidence of any widespread vasoconstriction during or immediately preceding a seizure. Mistaken conceptions have arisen from the reports of untrained observers. . . ." However, the authors express the belief that there may be focal ischemia of an epileptogenic lesion producing fluctuating neuronal activity which spreads to other areas of the brain. During a seizure there is cessation of arterial pulsation, perhaps due to dilatation of the vascular bed of the brain. Local nervous discharge is followed by increased blood flow in the area involved as a result of the accumulation of carbon dioxide or other substances which dilate the arterioles. Though the authors deny the etiologic importance of widespread vasoconstriction, they stress the evidences of instability of the cerebral circulation, which "may well play an important rôle in the mechanism which leads up to the spontaneous discharges within the brain of the

epileptic but are not involved in the mechanism of the discharge" (page 186). "In idiopathic epilepsy there is a familial tendency which suggests an inherited cause and it seems quite possible that an important element in this cause is abnormal physiology of the cerebral circulation" (page 11).

The approximate space given to the principal portions of the book is as follows: localization and mechanism of seizures, 35 per cent; organic lesions and their surgical treatment, 27 per cent; examination (made up mostly of chapters on electroencephalography and psychometric testing), 23 per cent; discussion of essential epilepsy and medical treatment, 15 per cent. Thus nearly two thirds of the book deals with problems of anatomy, pathology and surgical treatment of the brain, problems to which the authors have made important contributions. These sections are above the reviewer's criticism.

The first sentence in the book reads: "During the earlier stages of the preparation of this manuscript it was our firm intention to deal with focal epilepsy and to elaborate only those aspects of it which interested us, with no thought of encyclopedic treatment." It seems to the reviewer that the authors' first thought was their best. The encyclopedic treatment dilutes the quality of the book. The chapters on essential epilepsy are routine repetition of what others have found, without the sauce of discovery or the authoritative evaluation of conflicting reports. Furthermore, the addition of this subject disturbs the balance of the book. Essential epilepsy is too large a dog to be wagged by a cicatricial tail. Not anatomy and pathology but physiology, physics and chemistry hold the answer to the ultimate cause and cure of seizures. The reviewer believes a polished monolithic monograph, "Cerebral Localization in Focal Epilepsy," followed after a time by a monograph on essential epilepsy, would have served the diverse needs of the medical public better and would have provided a more enduring monument to intelligent toil.

The book has a certain lack of sequence and integration. Two explanations occur to the reviewer. First, the authors state they regard focal and essential epilepsy as distinct diseases so far as their fundamental etiology is concerned. One form is not transmitted to offspring; the other may be. One is solely the result of injury to the brain; the other is assumed to be caused by a circulatory toxin (page 471), a hypothesis which has only the weight of hoary tradition. In spite of this basic cleavage between the two forms of epilepsy, observations on focal or electrically stimulated seizures are projected onto essential epilepsy. Also, chapters dealing with the two subjects are intermixed. Thus the chapter headed "Results of Radical Treatment of Atrophic Epileptogenic Lesions" precedes by eight chapters that on "Surgical Therapy of Epileptogenic Lesions." Second, there are numerous repetitions. Thus, a certain half page table appears in four different places (pages 14, 61, 432 and 458) and another in three (pages 20, 321 and 457).

The authors have called on two of their colleagues for specialized chapters. The important subject of electroencephalography is well covered in the 75 pages which Herbert Jasper prepared. His complicated classification of brain waves, based primarily on the portion of the cortex involved, and only secondarily on the frequency of the waves, is presumably of service in the study of cases in which the thought of possible operation is uppermost. He does not seem to realize that the term dysrhythmia may be applied to waves which are too fast or too slow but are regularly spaced. Many interesting observations are recorded, especially the case (page 426) in which records were made from electrodes placed deeply in the brain. The lessons of this new technic have not percolated into the fiber of the whole book. Thus, in spite of electroencephalographic evidence that automatism in the epileptic patient is, like other seizures, accompanied throughout by abnormal cortical discharges, the authors cling to Hughlings Jackson's statement that the automatism is a postconvulsive phenomenon, a discharge of released lower centers resulting from exhaustion of discharged higher (cortical) centers. They give little credence to the possible influence of a preexisting constitutional dysrhythmia which activates an acquired epileptogenic focus.

The wife of the junior author, M. R. Harrower-Erickson, has a careful review of the intelligence and personality of epileptic persons and her own results with the use of the Rorschach test. She believes a peculiar personality, when present, is the result of injury to the brain or of environmental factors. The important subject of psychologic treatment receives scant attention here or elsewhere in the book. Also, there is disproportionately little advice about the day to day problems which arise over education, employment and social contacts.

The reader's evaluation of the relative importance of neurosurgery in epilepsy would be enhanced by a statement of the proportion of patients who, after study, were advised to have craniotomy or had it. The authors have not made an analysis of the family history of epilepsy of their patients with the symptomatic form; yet they tell these patients that they have no reason to fear epilepsy in offspring. What, by the way, is the meaning of the sentence which concludes the discussion of inheritance of epilepsy? "Epilepsy occurs early, and many conclusions have been drawn, which result in injustice to individual sufferers" (page 308). The authors advocate a housecleaning of terms. They would discard "grand mal" as ambiguous and use "ictus infratentorialis" for cerebellar fit. They would substitute "psychical, or sensory, precipitation" for psychic or reflex epilepsy but do not substitute "cicatricial precipitation" for traumatic epilepsy.

Though a book which has 623 pages, 163 illustrations and 202 case reports and weighs 3½ pounds (1,530 Gm.) may be large for the average physician's pocketbook, its size is in keeping with the problems of the brain and of epilepsy. The study and understanding of epilepsy has made tremendous strides in the last few years. Books on the subject available to the medical profession are sadly out of date. The present volume is a successful attempt to bring new knowledge to the medical profession. Though of greatest interest to neurologists, neurophysiologists and surgeons, it deserves a wide professional acceptance.

Science and Sanity: An Introduction to Non-Aristotelian Systems and General Semantics. By Alfred Korzybski. Second edition. The International Non-Aristotelian Library Publishing Company. Price $6. Pp. 806. Lancaster, Pa.: Science Press Publishing Co., 1941.

No thoughtful scientist would quarrel with Korzybski's thesis that one must give up the outworn modes of expression in terms of either . . . or, in stultifying dichotomies such as "mental or physical," "functional or organic." These limited ways of thinking have done much harm to sciences, especially to psychiatry. Korzybski would have all learn to apply a multiordinal mechanism of evaluation. He says:

> "If we stop to reflect, however, it seems obvious that those who are trained in two-valued, macroscopic, '*objective*,' aristotelian orientations only, are thoroughly unable to have modern, electrocolloidal, sub-microscopic, infinite-valued, *process* orientations in life, which can be acquired only by training in non-aristotelian methods."

By this he means, it seems to me, that dualistic philosophies will not work in the twentieth century. Human bodies and what they do and experience cannot exist separately. Dividing objects into elements and analyzing them is no longer scientific in 1942, because it is known now that structure itself is to be defined dynamically. Structure, function and mental experience can no longer be looked on as the three elements of a man. The advances in electrocolloidal physics show that elements exist only relatively. In describing any phenomenon one must be pluralistic, take in all the pertinent facts and extend the formulation. In American neuropsychiatry such men as Meyer, Herrick, Jelliffe and White have known and taught this for years. But Korzybski gives them little credit and rushes in with his discovery of "general semantics" as a science, making the whole subject too complex. His enthusiasm runs away with him.

His book called "Science and Sanity" is appearing in a second edition, like the first except for a fifty page introduction. The title might better have been "Monomania with a Scientific Camouflage." Too long has the medical reader

swallowed badly prepared fodder and tried to like it just because it was difficult. Much of the book is actually incomprehensible and all of it is wordy. In plan, style and execution it shows endless verbosity, distractibility, poor judgment and speculation taken for fact. The introduction to this edition is an example of the first; distractibility is well exemplified in the political diatribes on pages XXXVIII and XLII. The dedication pages, where 55 selected men are named, and the list of the "International Non-Aristotelian Library," facing the title page, are examples of poor judgment. Of this list, one volume, the present one, is "already published"; eleven volumes are "in preparations" and forty-five volumes, with names of authors to be announced later, are planned! A statement like "it is fundamental for 'emotional' balance to have 'normal' blood pressure" (page XXVII) simply is not true. Many people with abnormal blood pressure have perfectly good emotional balance. Again the author states, "In many instances serious maladjustments follow when 'hate' absorbs the whole of the affective energy of the given individual." In twenty years' practice the reviewer has never seen a case in which one type of emotion absorbed the whole affect. The statement, "It is well known that . . . arthritis, dental caries, migraine, skin diseases, alcoholism, etc., . . . have a semantogenic origin" is so preposterous that it needs no comment.

What makes one skeptical as to the soundness of the whole book is to come across a passage like this:

> "The deeper problems of neurological mechanisms enter here. If we orient ourselves predominantly by intension or verbal definitions, our orientations depend mostly on the cortical region. If we orient ourselves by extension or facts, this type of orientation by necessity follows the natural order of evaluation, and involves thalamic factors, introducing automatically cortically delayed reactions. In other words, orientations by intension tend to train our nervous system in a split between the functions of the cortical and thalamic regions; orientations by extension involve the integration of cortico-thalamic functions.
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> "Orientations by extension induce an *automatic* delay of reactions, which *automatically* stimulates the cortical region and regulates and protects the reactions of the usually over-stimulated thalamic region."

Many conclusions of the author depend on this formulation of neurology; yet the mechanisms described here as known are, to say the least, highly speculative. The reviewer admits he cannot understand the chapters on mathematics, colloidal behavior, etc., but when he runs into such speculative flights in the parts of the book he does know something about, he is unavoidably suspicious of the statements made in other chapters.

Anoxia: Its Effect on the Body. By Edward J. Van Liere, M.D., Ph.D. Price, $3. Pp. 269, with illustrations and index. Chicago: University of Chicago Press, 1942.

This small volume constitutes a useful outline of the many aspects of anoxia as it affects various organs and activities of the body. The material is clearly presented, and the references are in general excellent.

The chapter on the effect of anoxia on the nervous system, which is likely to be of particular interest to readers of this journal, is perhaps less authoritative than other chapters of the book. One has the impression that it was written from the literature, rather than from experience. It follows rather closely the compendiums of McFarland, Wolff and others but omits the important volume of the Association for Research in Nervous and Mental Disease on the circulation of the brain, and the recent work of the Gibbses, Lennox, Nims, Himwich and others on the utilization of oxygen by the brain under varying conditions. Carbon monoxide poisoning is presented as a condition due purely to anoxemia. Other minor deficiencies might be pointed out, but on the whole the collection of information is valuable and timely.